QUINTILES®

The Art & Science of Evidence

Rare Disease:

An integrated, patient-centered approach to research and commercialization

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Introduction: Cracking the code on rare diseases

Transform the lives of patients and their families

Although rare diseases individually affect very few patients, the collective impact is staggering. Globally, the list of rare diseases has grown to approximately 7,000, and 350 million people are living with a rare disease.[1] These diseases are serious, often life-threatening, and approximately half of those affected are children. The lack of available treatments leaves patients and their families searching for new options and new hope.

Regulatory incentives such as the orphan products designation and the availability of Pediatric Rare Disease Priority Review Vouchers have increased the interest in rare disease research. But with each potential new therapy, biopharma companies are charting new paths through clinical development, with limited disease knowledge, complex regulatory pathways, few suitable patients and unknown obstacles ahead.

Quintiles is an experienced partner who can help biopharmaceutical companies simplify the complexities of rare disease studies to speed new treatments to market for patients and their families. Through our experience conducting 245 rare disease studies since 2011, Quintiles has developed a comprehensive yet flexible solution to these complex and challenging studies. At the core is a specialized team with rare disease experience and therapeutic expertise that works work with you to identify the specific challenges of your study and then develops tailored patient-centric approaches to deliver on your goals.

"The Art & Science of Evidence – Rare Disease: An integrated, patient-centered approach to research and commercialization" is one in a series of compendia featuring blogs and bylined articles from Quintiles' experts. This collection highlights some of our recent thinking on how to better conduct rare disease research through patient-centric approaches to inform trial design and enhance the therapy's overall value story.

Kid talk

Cynthia Jackson, DO

Tragically, the greatest proportion of the population suffering from rare diseases are children. There are approximately 7,000 rare diseases[2] identified in the United States, and about 80 percent of these diseases are genetic – meaning people spend their entire lives dealing with the disease.

As a result, it is estimated that half of all rare diseases affect children. It is interesting to note that although individual rare diseases are uncommon, collectively they affect more children and families than most people realize and my family is no exception. My 5-year old nephew suffers from idiopathic pulmonary hypertension diagnosed when he was 4 months old. He has benefited significantly from medications that had been previously studied in pediatric clinical trials but the overall impact to his and his family's lives cannot be understated.

Thus, when we talk about research aimed at patients with rare diseases, we need to spend time talking about the unique needs of pediatric patients and their families who will certainly make up a significant portion of trial participants. Pediatric patients add challenges over and above those researchers face when designing trials to address rare diseases. Unlike adult-only trials, recruiting children for clinical trials in general is more complex and must take into account the needs of the child as well as the parents and family. Some of those factors include distance to the trial site involving travel and overnight stays, number of trial mandated visit, number and frequency of blood draws, length of study visits and other procedures which may involve anesthesia. Although these considerations are also important with adult-only trials, the logistics of family involvement require a different thought process.

As an industry we must not let these obstacles slow us down. Instead, we need to be more strategic in the way we plan for, design and ultimately execute these trials. Central to all of this is to effectively engage with the patients and their families in the early planning process. Leveraging patient and family communities will only improve the overall strategy and ultimate success of the trial.

- **Collaborate.** To begin with, researchers must think strategically about how to engage with physicians and patient advocacy groups as they design their trials. In most cases, there are only a handful of experts treating patients for a specific rare disease, so getting them on board as stewards of your trial has to be a top priority – otherwise the trial may face costly recruiting delays. Likewise, patient advocacy groups also can be a strong voice in fostering conversations about potential trial participation.

Unlike adult-only trials, recruiting children for clinical trials in general is more complex and must take into account the needs of the child as well as the parents and family.

- **Improve clinical trial design**. Researchers must also address the risk/benefit scenario that parents will consider when deciding whether to involve their child in a trial. Even if families are aware of trial, and encouraged to consider participation by their pediatrician or patient community, they are less likely to participate if they think their child's care will suffer. Placebo designs are especially challenging and require careful discussion and a thorough understanding on the part of the patient or family. Often times, these designs compare standard of care versus the study drug which allows the patient usual and customary care if they are randomized to placebo and not a withdrawal of therapy. A conversation with the study physician and the families/patients can clarify the subtleties of the design and address any concerns. Additionally, less common design can be considered such as crossover trials that allow patients to serve as their own control. This shifts the value proposition making participation more palatable to parents. Such trials may require early

communication with regulators to be sure the design meets their requirements. Early collaboration and buy-in to these designs could serve to enhance interest and participation by patients and families yielding successful trial completion and viable data leading to new therapies.

- **Leverage registries.** Finally, patient registries are a vital part of this process, for researchers, patient groups, and regulators. Registries provide these groups with a way to gather and review data about the disorder, and to create a database of patients who might be candidates for current and future trials. The National Organization for Rare Disorders (NORD) argues[3] that patient registries should be recognized as a global priority in the field of rare diseases as they support "fundamental clinical and epidemiological research, and post-marketing surveillance of orphan drugs and treatments used off-label."

Although you can't eliminate the challenges of recruiting pediatric patients for rare disease clinical trials, a little up-front planning keeping the patients and families in the loop along with cross-collaboration can help overcome many of the biggest obstacles. After all, the ultimate goal is to develop new medications based on good trial data, which could have life altering consequences for patients and families dealing with rare conditions.

Researchers must think strategically about how to engage with physicians and patient advocacy groups as they design their trials. In most cases, there are only a handful of experts treating patients for a specific rare disease, so getting them on board as stewards of your trial has to be a top priority – otherwise the trial may face costly recruiting delays.

A patient-centric approach to rare disease recruiting

Jeanne Hecht, MBA, PMP

How putting patient needs first improves patient engagement, and makes recruiting a more pleasant experience for everyone involved.

Recruiting is a difficult and uncertain process, especially when it comes to rare disease trials. But it can be a lot more productive and efficient if trial designers look beyond what they are trying to accomplish in order to think about what they need to do to make the trial appealing to patients.

Patients with rare diseases often have limited treatment options and less access to information about current research and trial opportunities, which means researchers need to work harder to identify these far flung patients, and to create an environment where they will want to participate in the trial opportunity.

If patients don't know about a trial, if they don't trust the researchers/company running the trial, or they think the protocol will too painful, time-consuming, or too far away, the physicians will lose them before they fill out the first form. And if an organization is trying to recruit from a very small, widely dispersed patient population that loss equates to time and money wasted in the drug development cycle. It seems like a simple approach, but too often researchers get so caught up in what they want to accomplish with a trial that they forget to think about what the patients will need for them to even consider participating.

Adapting the trial design to a more patient-centric approach for rare disease trials doesn't require a major overhaul. Researchers just need to shift their focus and think about the trial through the eyes of the patient and their caregivers. Taking this view will help them make small changes to the trial design, and avoid the mistakes that might otherwise cause them to miss out on effective recruiting opportunities.

Collaborate with patient support groups

Whether a patient is newly diagnosed with a rare disease, or a long-time sufferer looking for alternative treatment options, the first place they are likely to turn is a patient support group. These groups help them feel like they are not alone, and give them a trusted place to find information about trials, resources, and education about treatment options. These groups can be particularly important for sufferers of rare diseases, who may feel isolated and frustrated by a lack of options. Yet, because there are so few sufferers, these groups are often poorly funded, and may struggle to find the resources or expertise to support their members or to build-out their web presence.

This creates a great opportunity for biopharmaceutical companies and research teams to lend a hand. Leveraging and supporting these groups with research materials, educational support and other patient tools will help the patient community become better informed about their disease and about the research in the space. It will also help them begin to build a trusting relationship with the people most likely to participate in the trials, or to broadcast information to those who might.

Identify barriers to participation

With small and widely dispersed patient populations, researchers focused on rare diseases cannot afford to lose any potential patients. To reduce this risk, researchers should take the time to interview patients, care givers, and thought leaders in the disease space about the biggest obstacles to participation, then work that feedback into the trial plan and protocol. Some of the challenges may involve fears about medical uncertainties or discomfort, while others may be more logistical. Based on these interviews, researchers may find that making small changes – such as scheduling evening appointments or offering on-site childcare– is enough to make the trial more accessible for hesitant recruits.

Build sites around patients

When dealing with a dispersed patient population, which is almost always the case with rare disease research, trial designers need to be more strategic in the way their build their trial infrastructure. Instead of opening 200 trial sites and hoping patients will turn up, start by identifying down potential patients then creating trial sites around them. This eliminates two of the biggest barriers to recruitment in a rare disease trials – geography and trust. By bringing the trial to patients, the research team makes it physically convenient, while enabling them to be treated by their own physicians.

This approach may require some additional time and resources to ensure these sites are trial ready. Trial leaders will likely need to train doctors and support-staff on good clinical practice (GCP) standards, using a program like Quintiles' Site Training eLearning Program (STeP). They may also need to upgrade basic infrastructure, like adding locked cabinets and temperature controlled storage units, and potentially hire a few support staff to ensure the trial is run correctly. But compared to the cost of opening dozens of trial sites with low numbers of participants, this approach will still cut time and cost from the recruiting and research process. It will also help the biopharma company expand its network of treatment sites and trained investigators for future trials.

Leverage rapid study placement approaches

Rapid study placement techniques are about making sure all the pieces are in place to engage the rare disease patient as soon as they agree to participate. To do that, research teams should:

1. Ensure regulatory pathways are well documented and that the protocol has been reviewed by a Central Institutional Review Board4 (IRB)/ethics to be sure it is ethical, provides potential benefits, and does not cause unnecessary harm to participants.
2. Have an approach in place for developing the start-up documents and processes needed to make new sites operational, including templates for data collection, toolkits and recommendations for defined SOPs for use with the site.
3. Ensure that a training program is in place for sites that are new to research (e.g., Quintiles' STeP).
4. Ensure that all human resources are trained and ready to go as soon as the sites are up and running and as soon as patients are recruited.
5. These approaches are not necessarily designed to engage patients, rather they are to ensure that once the research team has identified and recruited patients for their rare disease study, they don't lose them due to unnecessary delays and hiccups in your trial operation.

Remember, when it comes to patient engagement, you need to be ready when they are!

Faster recruiting for rare disease research

Building relationships with key opinion leaders can cut months from the trial process

Lynne Hughes, B.Med.Sci., PhD, PMP

Rare disease research can be particularly difficult for a number of reasons, but one of the biggest challenges is recruiting. When you are developing a drug to treat a very small population of patients, or a tiny subsection of a larger population, it can feel overwhelming to even imagine how you will set up sites and attract enough patient to make the research work.

The truth is, there is no silver bullet, but there are strategies researchers can follow to make this process faster, easier, and a lot less expensive. As we acknowledge Rare Disease Day, I think it is fitting to share this best practice example of how to one big pharma company took a different approach to recruiting, and how it paid off.

Investigate the investigators

We recently worked with a biopharma company that was preparing to launch a Phase I study for patients with an extremely rare form of an already rare disease. The targeted patients, who have a unique gene mutation, represent just two percent of the entire disease population, and the sponsor was uncertain about how to identify and recruit enough patients to support the goals of the trial.

Rather than opening dozens of sites around the world and hoping the right sub-group of patients would turn up, they took a more strategic approach by conducting an in-depth review of all of the literature published about this disease

and the specific patient population to identify key opinion leaders globally. The review, which began with a Google search, identified dozens of investigators whose published work suggested that they were focused on the disease and would likely have access to patients with this specific genetic mutation. The planning team then reached out to all of these investigators to determine who among them had a keen interest in treating patients with this specific mutation – versus those who'd only experienced a few patients in the broader spectrum of their work. In some cases they found physicians listed on a peer reviewed article who were only accessory authors but who could suggest the best investigators to connect with.

Rather than hoping the right sub-group of patients would turn up, a study took a more strategic approach by conducting an in-depth literature review and a look at the specific patient population to identify key opinion leaders.

After narrowing the search, they invited the top 20 investigators from around the world to join an innovation team and hone the protocol and recruiting process, and identify as many pre-qualified candidates as possible.

Most of these investigators had no experience with trials or trial design but they had been working closely with these patients, bringing valuable insight to the project. By working together, the biopharma research team and the investigators were able to educate each other about what this patient population would want from a trial, and what criteria were required to make the trial results meaningful.

One of the key outcomes of these collaborative conversations was the idea that because these patients were likely to die from the disease before the drug came to market, they would be more open to participating, if they would be given the opportunity to use the drug as an open label prescription, after initial research demonstrated enough safety data to warrant the option. Together, the research team and the investigators created a protocol that met everyone's needs, and the investigators helped the research team target their recruiting efforts.

This initial research stage took roughly a year, but enabled the biopharma company to recruit patients to the trial much more quickly and effectively than if they had followed a more traditional approach.

A new protocol

This example offers a valuable lesson about the importance of thinking more strategically about the trial design process in rare disease research. It also highlights the benefits of working with key opinion leaders to inform the trial design and to connect with patients who might be eager to participate in a trial designed to ease their suffering.

Careful planning, which may involve moving away from traditional operational models, enhances the opportunity for a unique and successful operational strategy.

It requires trial sponsors to set aside additional time at the beginning of the project to identify these investigators and educate them about the trial process. They also must be open to learning from these investigators what patients will need from a trial and how they can improve their protocol to meet those needs. But that time spent up front is more than made up for in savings down the line. If researchers can identify where to find these patients, and connect with them directly through their physicians, they can recruit them more easily, and set up sites that will be most likely to serve the largest number of patients in the shortest amount of time.

This is just one example of how rethinking the traditional trial design methodology can help rare disease researchers overcome some of the barriers to progress. It also underscores how important it is to build a targeted operational strategy and structure for rare disease clinical trial conduct. Careful planning, which may involve moving away from traditional operational models, enhances the opportunity for a unique and successful operational strategy.

Rare disease research is becoming an increasingly attractive development path for biopharma companies around the world. The biopharma companies that are willing to adapt their methods, partner with global experts, and embrace new ideas will be the ones to see the most success in this space.

Patient advocacy groups: A critical resource for rare disease trials

Jeanne Hecht, MBA, PMP

When it comes to recruiting patients for rare disease clinical trials, patient advocacy groups can be a researcher's best friend.

Patient advocacy groups are one of the first places patients and their caregivers go to when they are first diagnosed with a rare disease, and these patients come to rely on these groups to provide them with information, support, and camaraderie as they live with that disease every day.

As a result, these advocacy groups should also be seen as an invaluable resource for researchers, both as a portal to identify and network with potential trial participants, and a knowledge center where researchers can further educate themselves about disease treatment patterns, obstacles patients face, and their expectations for solutions from the biopharmaceutical industry.

One of the biggest challenges rare disease researchers face is recruiting patients from an already small population. However, because treatment options are often very limited, if you can find these patients they are usually far more open to participating in a trial than someone with a condition for which there are already many treatment choices. Engaging with patient advocacy groups is one of the best options for connecting with these patients. But to get the most value from these relationships you have to demonstrate your willingness to partner with these groups, before you can win their trust.

5 tips for engaging patient advocacy groups

1. **Start early.** As with all relationships, establishing trust doesn't come quickly. You need to invest time and resources into building a rapport with the advocacy group long before your trial begins. You can do this by participating in online conversations at the group's website, fielding questions from patients, providing

source materials, and offering experts for webinars, conference sessions, or other knowledge-building events. The more you can establish yourself as a reliable resource and thought leader, the more the community will turn to you for answers about their disease.

2. **Ask questions**. If you want patients to participate in your trial, ask them what would make it more appealing. Often the biggest recruiting obstacle for patients are things like appointment timing, logistics, fear of too many needle pricks, and outdated protocols that exclude patients unnecessarily. The more you talk to patients through the advocacy group about their expectations, barriers, and desired outcomes from a trial, the more you can customize your protocol to appeal to their needs.

3. **Underwrite their efforts.** Patient advocacy groups come in all shapes and sizes, from two-person outfits to major national organizations. Regardless of their size and status, however, they are all non-profit organizations and they are always looking for help. That doesn't mean you should just cut a check and walk away. To get the most value from investing in an advocacy group, tie your donation to a specific cause or event, and back it up with human capital. That could mean sponsoring a conference and providing expert speakers, jointly delivering a webinar, or offering to produce educational materials for the group. In this way you help them meet their goals while further cementing your standing as a trusted leader within their community.

4. **Get the word out.** Let the advocacy group know as soon as you have a trial planned, and ask for their help to connect with potential patients and physicians to support your recruiting efforts. For many of these sufferers, clinical trials are the best opportunity to receive treatments that will improve their quality of life – if they hear about it from someone they trust. If you've put in the effort to build a relationship with the patient advocacy group, they can become your loudest and most valuable champion. One of the primary goals of an advocacy group is to encourage research into new treatment opportunities, and to support efforts to move these trials forward. If they believe that you have their best interests at heart, they will help you achieve your goals.

5. **Follow up.** Patients with rare diseases are always eager for information about their disease, and impending treatments. Sharing information about a trial's progress, outcomes and next step will keep the community engaged with your work, and prime the pump for your next recruiting effort.

How a parent advocacy group swayed the FDA

Proving the value of bringing the patient voice into rare disease trial design

Susan Tansey

In the summer of 2015, rare disease research achieved an exciting milestone: for the first time ever the U.S. Food and Drug Administration (FDA) used a proposed draft guidance[5] prepared by a parent advocacy group as the basis for its own draft guidance for industry.

The document, "Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment,"[6] is intended to assist companies in the clinical development of drugs for the treatment of Duchenne muscular dystrophy and related conditions. X-linked Duchenne muscular dystrophy (DMD) is a progressive and fatal muscle-weakening condition that affects approximately 10,000 to 15,000 people in the U.S., mostly men and boys. Specifically, this guidance addresses FDA's current policy thinking regarding the clinical development program and clinical trial designs for drugs to support an indication for the treatment of one or more of these dystrophinopathies.

The suggested guidance was prepared by Parent Project Muscular Dystrophy (PPMD)[7], an independent advocacy group, which assembled a committee of parents, scientists, drug company executives and clinicians.[8] Their goal: accelerate drug development for Duchenne, and provide perspective on what makes sense in a trial protocol to meet the needs of regulators and patients. The group encouraged FDA to expand use of accelerated approval for therapies, and to expand the scope of acceptable endpoints. For example, a hallmark of these trials is a six-minute walking test as a primary measure of a drug's success. But this tests eliminates most children under the age of seven, and all of the patients who can no longer walk from participation. They argue that using a test that eliminates such a broad

swathe of the patient population is counterproductive for sponsors and frustrating for parents who are desperate to find a cure. Instead they suggested other scientifically relevant tests to measure success, including time to rise from the floor, and pulmonary and cardiac measures.

The documents also suggest giving greater weight to the benefit/risk preferences of patients and caregivers in the case of pediatric illness. To highlight the stark reality of this this point, one parent of a 17-year-old with Duchenne's wrote[9]: "Duchenne has taken so much from him that I would consider treatments that would allow him to keep the function he has now, even if there are some risks. This may not have been true 10 years ago." She goes on to argue that the concept of risk vs. reward changes over time, and that older boys who need treatments as fast as possible are probably more willing to accept more risk for what may seem a little reward. "We are willing to take a chance," she said. "It's better than no chance at all."

It is this kind of insight that statisticians won't find in databases of research, or peer reviewed articles, and it underscores the importance of putting the voice of the patient into the trial design.

A parent advocacy group encouraged FDA to expand use of accelerated approval for therapies, and to expand the scope of acceptable endpoints.

Listen

Patient advocacy groups are a strong voice in the rare disease research community and valuable allies for biopharma companies. The most powerful among them raise money to support research[10] they deem important, collect data in online patient registries,[11] and are willing to offer feedback to regulators and researchers on the "patient important outcomes" that can determine participation in a trial.

When biopharma companies take time to listen to their advice, and factor their feedback into the trial design, they may discover that this helps them craft a protocol that is more acceptable to patients and parents. This results in a more efficient recruitment process and higher levels of retention, which in turn cuts time and costs while improving the odds of success.

However, to harness the value these groups bring to the table, researchers need to embrace a culture change in the way they plan and manage trials. It can be easy to dismiss the voice patients and caregivers in favor of scientists and statisticians, but neither group of experts has all the answers. While a parent may not be aware of all of the intricacies involved in the regulatory approval processes, so too do statisticians often miss or ignore patient important outcomes, like the fact that maintaining hand-eye coordination is important to Duchenne patients even if they can no longer walk, or not putting children through invasive and seemingly unnecessary procedures as a condition of enrollment in a trial.

It can be easy to dismiss the voice patients and caregivers in favor of scientists and statisticians, but neither group of experts has all the answers.

Change is hard, especially in the biopharma world, but making room for the patient's voice will benefit these trials down the line. When it comes to rare disease research, any change that can drive effective treatments to market faster should be warmly embraced by everyone involved.

Adaptive pathways offer hope to meeting patients' needs faster

Stella Blackburn, MBBS

The European Medicine Agency's Adaptive Licensing Pilot project is a uniquely collaborative process designed to allow early and progressive patient access to medicines which address unmet medical needs.

While the global burden of disease is complex and varied across geographies, ages and therapeutic areas, the unmet medical need among patients with rare diseases remains much higher than most other patient populations. Patients, physicians, regulators and researchers working to advance the development of treatments for rare diseases face numerous challenges; one of which is the small patient populations that make traditional approaches to drug development and clinical trial evaluations nearly impossible to follow.

One of the most heartbreaking outcomes of this reality is the dearth of treatments addressing rare diseases. There are approximately 7,000 different types of rare diseases,[12] affecting more than 350 million people worldwide[13] – half of them children. Even if a biopharma company begins development of a promising drug, it can be years before those treatments hit the market, which is often too late for many patients to benefit. But the European Medicines Agency (EMA) is attempting to make their future a little bit brighter.

Two years ago, EMA launched the adaptive pathways[14] pilot program, a uniquely collaborative process designed to allow "early and progressive patient access to a medicine" for drugs that promise to meet unmet medical needs in the marketplace. EMA calls it "an opportunity for early brainstorming discussion among all relevant stakeholders, including regulators, companies Health Technology Assessment bodies (HTAs) and patient representatives, to explore ways to optimize development pathways and potentially accelerate patients' access to medicines."

The pathway allows for rapid approval and is based on three principles: 1) iterative development through either staggered approval going from a narrow restricted initial target population to wider patient populations or by reducing the uncertainty surrounding an initial authorization with early or surrogate endpoints; 2) using real-world data to supplement clinical trial data and 3) involvement of patients and health technology assessment bodies. Once developers can prove a positive benefit/risk scenario they can secure approval at an earlier stage, then continue to collect real world evidence from patients using the drug to validate efficacy in a real world setting. The hope is that this innovative program will shorten the time it takes for patients to gain access to desperately needed drugs, while still requiring biopharma companies to complete the full regulatory process.

EMA has accepted 20 proposals to date for Stage 1 discussions. Of these, 11 were selected for Stage II "in depth" meetings. Companies which have announced their involvement in the program include: Bluebird Bio,[15] a clinical-gene therapy company pursuing approval for LentiGlobin BB305, a candidate for the treatment of beta-thalassemia major; Immunocore Limited,[16] a biotech company seeking conditional approval for IMCgp100, a biologic for the treatment of metastatic uveal melanoma, a rare and fatal disease with few available treatment options; Pluristem Therapeutics,[17] a developer of placenta-based cell therapy developing a product that targets a subgroup of patients with critical limb ischemia (CLI); and GSK who have two products working together to treat systemic amyloidosis.

As of early 2016, EMA was still seeking applicants[18] with "well-developed" proposals to take part in the initial pilot, though getting accepted and making the most of this adaptive pathway opportunity will take some careful thought and planning. For drug developers interested in exploring this option, here are five steps to improve your odds of success.

1. **Determine whether your drug meets the criteria.** Candidate selection is a major piece of the adaptive pathway process. EMA is looking for innovative drugs that fill an unmet need in society usually associated with a rare or orphan disease. Companies need to be thinking about life-cycle development.

2. **Consider building a registry very early on.** Once a drug receives early conditional approval, researchers will need to continue to collect real world evidence from users about how the treatment works, potential side effects, and how the drug compares to any existing treatments, or none at all. However, companies that build patients registries at the beginning of the development process can use them to provide data on the natural history of the disease

possibly enabling single arm trials – an important option for rare diseases with no current effective treatment. Patients can be rolled over from trials into the registry to gain valuable long term data.

3. **Engage early with EMA and HTAs.** One of the key components of the adaptive pathway model is to provide developers with an opportunity for early brainstorming discussions with all relevant stakeholders, including regulators, HTAs,[19] and patient representatives. These brainstorming sessions are meant to provide all participants with ideas for optimizing development pathways and potentially accelerating patients' access to medicines, including the evidence you will need to gain both approval and reimbursement for your drug. Developers who are interested in following this pathway are encouraged to engage early on with stakeholders to share their results, gather feedback on next steps, and to use that feedback to adapt their development process and decision-making for the product. One of the biggest challenges in this process is choosing which regulators and HTAs to engage with. In contrast to the benefit-risk assessment carried out by regulators, HTA bodies compare the relative effectiveness of medicines so they can provide recommendations to their member state on whether the treatment should be paid for or reimbursed by the healthcare system. It is unrealistic to think you can meet with all of the HTAs. Instead be strategic in who you chose to work with.

4. **Ask specific questions.** You may only have a brief opportunity to engage with HTA leaders and regulators, so don't waste it asking for information you could find on their website. Do your research and be ready to ask detailed questions that pertain to your drug, and the approval and reimbursement process.

5. **Think about your broader license continuum.** The adaptive pathway is conditional for specific uses and user groups, and thus companies must have plans for augmenting the data following the initial approval. You have to keep working toward full licensing goals which means having plans for continued collection of data to reduce the uncertainty around estimations of the benefits and risks – particularly if the initial approval was based on small patient numbers and/or surrogate endpoints.

The adaptive pathway program could become a tremendous opportunity to speed key drugs to market – especially for rare diseases given the small patient size and large unmet medical need. But this innovative approach to regulatory approval does not in any way lessen the need for due diligence, careful planning and strong stakeholder engagement. The drug developers who put the time and expertise into the planning process will be best positioned to take advantage of this fast track opportunity to bring new drugs to the patients who need them most.

There are approximately 7,000 different types of rare diseases, affecting more than 350 million people worldwide – half of them children.

Social listening in rare disease research

Jessica Perry

How understanding online activity of potential clinical trial patients can improve rare disease recruiting.

Data analytics, social media and online resources are making recruiting for rare disease trials just a little bit easier.

Recruiting for rare disease trials is particularly challenging given that most rare diseases impact very small and widely dispersed patient populations. Finding those patients and facilitating their awareness of the study can be particularly arduous. Companies may open dozens of trial sites that only recruit a handful of patients – if any at all – and they often spend years trying to meet minimum recruitment numbers, which is expensive, time consuming and ultimately disappointing for patients and families anxiously awaiting new treatments to come to market.

Fortunately, data analytics and "social listening" is taking some of the guess work, and risk, out of this process by providing insights into what the primary considerations are for these patients. Social listening is a good initial step in helping to pull together the patient profile for a particular indication.

Tracking the patient journey

Social listening involves running an algorithm, or set of keyword-driven questions, to understand online activity related to a specific topic, or in this case, disease. For example, an algorithm might ask what people are saying on social media about Fabry disease[20] (a rare genetic lysosomal storage disorder). Analytics technology uses the algorithm to scan the internet for any related discussions about the disease on social media, patient advocacy groups, journal articles and any other relevant online sources. The results are then compiled in a report that includes statistics on the frequency of topics at various websites, excerpts of conversations and additional key words associated with the indication. Because rare diseases

have such small patient populations, a cluster of conversations from a specific website or advocacy group can be particularly meaningful.

Messaging and outreach

We have worked on many rare and orphan trials in which we have leveraged social listening to support the overall recruitment strategy, including trial messaging and outreach methods. Understanding the conversations that patients with a particular indication are having regarding a particular disease, as well as knowing the top websites that patients are viewing, helps us in the development of messages and images that would resonate with patients. For example, in one social listening report for neurofibromatosis, content theme results indicated that parents of newly diagnosed patients are struggling with where to find support, particularly as new mothers. This information along with understanding the top sites, such as parenting websites, support messaging development and location of trial awareness posts.

In some cases, we find the strongest conversations are happening on the websites or forums of one or two key patient advocacy groups for a particular indication. This helps us identify which groups have patients who would have potential interest in the trial. This information can also help in identifying potential key opinion leaders in order to network with experts who can provide assistance in recruiting efforts.

Recruiting for rare disease trials is particularly challenging. Fortunately, data analytics and "social listening" is taking some of the guess work, and risk, out of the process.

In other cases, we've had teams find that a disease has no strong advocates or support groups. This is particularly common in ultra-rare indications where there are so few individuals with the disease, little support or information is available to the patients. That information allows us to consider if building a patient community for the study will ultimately help engage patients and physicians in the space.

Early insights

Although not a key driver, social listening data can also be helpful in early protocol design of trials. Combined with additional sources such as physician insights, direct patient survey insights and site feasibility data, it can help uncover aspects

of treatment and trials that are most important to the patient. For example, what are the symptoms of a particular illness that are most discussed among patients? What side effects of current treatment options are most discussed and are patients demonstrating high activity in looking for alternative therapies? Understanding the answers to these questions can provide good insight into designing trials that are patient centered and often can be easily answered or confirmed through social listening.

Ultimately, taking the time to do social listening in conjunction with traditional data insights, prior to the start of a study and even prior to finalization of a protocol, assures that trials start on the right foot. That benefits the biopharma companies who want to cut time and cost from trials, but more importantly ensures the patients voice and needs are factored into the trial design.

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Bringing orphan drugs to market

Four critical issues to consider when launching a new therapy for a rare disease

John Doyle, DrPH, MPH

Some people assume that finding treatments for rare diseases offers little economic incentive for biopharmaceutical companies. If these diseases are so rare, the argument goes, who is going to buy the product?

But that is a misconception. Research into rare disease treatment can be quite lucrative. They actually have a large potential market size with high market growth rate compared with the overall prescription drug market. And the severity of unmet need and general lack of competition in these categories leave potential to charge a premium, making rare disease treatments an attractive option for biopharma.

Consider the facts:

- Roughly 30 million people in the U.S. and another 30 million people in the EU suffer from rare diseases. Even with more than 400 products on the market today and a number of new products being approved, there are still a lot of latent unmet medical needs.
- The U.S. Food and Drug Administration (FDA) and other governmental agencies now offer explicit economic incentives to develop orphan drugs as a way to encourage research and development in this important sector.
- This category is currently experiencing high market growth, with some estimates suggesting it will double the non-orphan drug prescription market in terms of compound annual growth rate for the next 5-10 years.

- The drug companies appreciate that there is a correlation in treating a severe unmet medical need and return on investment. This is an area where they can ensure premium pricing based on developing a premium product.

However, there are clinical, economic and humanistic challenges biopharma companies must overcome for any orphan drug to be successful.

There are four critical issues to consider:

1. **Value-based pricing**. Orphan drugs command premium pricing, but that pricing also draws added scrutiny from regulators, physicians and patients. Biopharma companies must remain cognizant of stakeholders' concerns, and price these products in a value-based way if they want them to be adopted.

2. **Ensuring coverage.** Many of the big payers in the EU and U.S. look at rare disease as such a small sample that they want to steer clear of making exclusive decisions about coverage, using step edits, prior authorization, or other types of payer controls to manage their risks. They are also pushing more costs to patients as a way to control utilization of the product. All of these issues need to be considered as part of the go-to-market plan. Biopharma companies need to strategize how they can ensure adequate coverage for the product across different payers.

3. **Providing access.** Coverage doesn't ensure access. Once a product is priced and coverage is optimized, they need to think about access and adoption. This includes making sure patients can access not only the drug, but also proper diagnostic mechanism, triage and centers of excellence focused on that rare disease.

4. **Adoption.** Once the price is set, coverage is granted and you are achieving access, you need to be sure the physicians and the patients are adopting the medication. A misconception persists that rare diseases "fly under the radar" in healthcare systems and thus don't warrant the attention of health technology assessments. HTAs and CER can provide evidence of value. However, unique challenges for rare diseases include lack of patients and data, and the fact that risk-benefit may be considered differently.

Many times we see a drop off in persistence with these medications, so biopharma companies should consider what go-to-market strategies will encourage adherence among patient populations.

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About the authors

Stella Blackburn, MBBS

Vice President, Global Head of Risk Management, Real-World & Late Phase Research

Dr. Stella Blackburn leads risk management efforts in North America, Europe and Asia-Pacific for the Quintiles real-world and late phase research group. In her role, Dr. Blackburn develops multidisciplinary benefit risk management services, reviews and assists customers with interpretation of pharmacovigilance legislation, and ensures compliance with regulations and best practices in the conduct of pharmacovigilance and risk management activities for the company's real-world and late phase research efforts.

With more than two decades of experience in the pharmacovigilance and pharmacoepidemiology fields, Dr. Blackburn joined Quintiles from the European Medicines Agency (EMA) where she served for more than 16 years in various roles, most recently as the EMA Risk Management Development and Scientific Lead. In this role, Dr. Blackburn was responsible for designing and implementing risk management public policy and processes used throughout Europe. Dr. Blackburn also worked with biopharmaceutical companies, government bodies and industry consortia to advance risk management and real-world research, including registry projects and public-private partnerships.

Before joining the EMA, Dr. Blackburn worked in hospital medicine and also spent more than 11 years in the pharmaceutical industry in a variety of leadership roles. Throughout her career, Dr. Blackburn has lectured around the world on pharmacovigilance and risk management and written chapters on the same topic in several textbooks and industry-related guides. Dr. Blackburn is also the past-President of the International Society of Pharmacoepidemiology. Dr. Blackburn trained in medicine at the University of Cambridge and the University of London Guy's Hospital Medical School. She earned her Master of Science in Epidemiology from the London School of Hygiene and Tropical Medicine.

She is a Fellow of the Royal College of Physicians of Edinburgh, the International Society of Pharmacoepidemiology and the Faculty of Pharmaceutical Medicine of the Royal Colleges of Physicians in the UK.

John J. Doyle, DrPH, MPH

Senior Vice President, Advisory Services

John J. Doyle, senior vice president, Advisory Services leads the Values & Outcomes efforts – working with Life Science companies to navigate the transformational changes in the health care marketplace from a population health perspective.

As the global health care system migrates from volume to value and outcomes-based medicine, Dr. Doyle's team of strategist partners with clients to diagnose, strategize, and illuminate a product's benefit-risk and economic profile tailored to a myriad of market stakeholders to drive healthcare system performance in an increasingly evidence-based environment. Functional areas of expertise include pricing and reimbursement, health economic and outcomes research (HEOR), and medical affairs.

Over the last two decades, Dr. Doyle has authored over 100 abstracts and original research articles in a variety of therapeutic areas, with special concentration in oncology. He has lectured for academic and commercial audiences in the U.S., Canada, Europe, Latin America, and Asia.

Dr. Doyle received a Bachelor of Science degree in Applied Economics with a concentration in the Life Sciences from Cornell University. He received a Master of Public Health degree and a Doctor of Public Health degree in Epidemiology from the Mailman School of Public Health at Columbia University, where he maintains an adjunct faculty position.

About the authors

Jeanne Hecht, MBA, PMP

Senior Vice President, Site & Patient Networks

Jeanne Hecht is Senior Vice President and Global Head of Site and Patient Networks at Quintiles, a position she was appointed to in October 2014. In this role, Jeanne is responsible for leading, implementing, and driving a site and patient network-centric global strategy that leverages leading-edge technology. In addition, she is responsible for leading a team that builds out patient recruitment implementation models, personalized medicine and disease specific networks, clinical partnering strategies and fit-for-purpose partnering models.

Prior to assuming this role, Jeanne was the Senior Vice President and Global Head of Sales at Quintiles. During her career with Quintiles, Jeanne has served in many roles across a number of disciplines and honed her international experience by residing in Singapore for almost two years to lead Quintiles' Asia Sales and Strategic Planning team. In this role, Jeanne was instrumental in the development and acceleration of growth within the domestic markets. Before moving to Asia, Jeanne served as Vice President, Strategic Accounts for Quintiles.

Jeanne has more than 20 years of experience in the healthcare industry and is also a certified Project Management Professional (PMP). Earlier in her career, Jeanne was a founding member of a company utilizing biomarkers for companion diagnostic purposes. The product was designed, branded and launched under her leadership as Vice President of Marketing and Sales.

Jeanne earned her Master of Business Administration and bachelor's degree in biology from the University of Michigan.

Lynne Hughes, B.Med.Sci., PhD, PMP

Vice President and Head, Neurology Center of Excellence

Lynne Hughes is vice president and head of Quintiles' Neurology Center of Excellence, where she develops evidence-based strategies to conduct clinical programs for customers. She also leads the Autism Center of Excellence, which provides therapeutic input and expertise for conducting trials in patients with autism spectrum disorders to improve their neurocognitive function.

A biopharmaceutical industry veteran, Dr. Hughes has worked in the industry for nearly 30 years, including 19 years at Quintiles. She possesses expertise in all areas of neurology, including Alzheimer's disease, multiple sclerosis, Parkinson's disease, epilepsy, acute care and pain. Dr. Hughes has been involved in the clinical trial development of many of the neurological therapies on the market today.

Dr. Hughes earned her bachelor's degree in Medical Sciences from the University of Bradford in Bradford, England. She completed her Ph.D. in Oncology and Cancer Biology at the University of Birmingham, in Birmingham, England, fully sponsored by Cancer Research UK. In addition, she is certified as a Project Management Professional.

About the authors

Cynthia Jackson, DO

Vice President and Head, Pediatric Center of Excellence

Cynthia Jackson, D.O., is vice president and head of the Pediatric Center of Excellence. In that role, she leads strategy and consulting around all aspects of pediatric clinical development. She also serves as a consulting assistant professor in the Division of Pediatric Infectious Diseases at Duke University.

Throughout her career, Dr. Jackson has served as a medical advisor for clinical trials in therapeutic areas related to pediatric patients, including asthma, allergies, migraines, nutrition and vaccines. In addition, Dr. Jackson has experience with infectious diseases indications such as antivirals, anti-HIV compounds, tuberculosis, vaccines, antifungals and antibacterials.

Prior to joining Quintiles, Dr. Jackson was the chief of pediatric infectious diseases at the University of Illinois-Chicago College of Medicine in Peoria, Illinois. As a clinical investigator, she has worked on antiretroviral, antifungal, antiviral and vaccine studies.

Dr. Jackson earned a doctorate from Des Moines University College of Osteopathic Medicine and completed pediatric residency at Western Reserve Care System in Ohio and a fellowship in pediatric infectious diseases at Duke University, as well as a research fellowship in retrovirology at Glaxo Wellcome.

Jessica Perry

Associate Director, Patient Recruitment Programs

Jessica serves as an Associate Director for Patient Recruitment Programs at Quintiles. She has worked in clinical research for over 12 years. Throughout her career in clinical research, Ms. Perry held roles on clinical study teams as CRA, Clinical Trial Leader and Clinical CRA manager. She joined the Patient Recruitment Programs team to support development of strategies using her in-depth clinical study experience with particular focus on Rare & Orphan diseases. Ms. Perry also sits on the Quintiles Rare & Orphan Disease Platform team.

Ms. Perry has worked on Phase II, III, & IV clinical trials and this experience spans the execution of clinical trials, from study start-up to project close-out and archival. Ms. Perry's therapeutic experience includes cardiovascular therapies, multiple sclerosis, depression, women's health, pediatric medicine, and infectious disease. She has supported multiple rare disease indications including hypophosphatasia (HPP), paroxysmal nocturnal hemoglobinuria (PNH), Fabry Disease and Molybdenum cofactor deficiency (MoCD) as well as development of overall rare disease recruitment practices. Ms. Perry also has expert working knowledge of FDA regulations, ICH guidelines, Good Clinical Practices and Standard Operating Procedures.

About the authors

Susan Tansey, MBChB

Vice President and Global Head, Medical Strategy and Science

Susan Tansey is Vice President and Global Head for Therapeutic Strategy having trained in pediatrics in the U.K.'s National Health Service specializing in respiratory pediatrics and neonatology. She joined industry in 1998 and has since worked in clinical development in several therapeutic areas including cardiovascular, vaccine research and oncology. She has developed a specific expertise in pediatric clinical trials and currently is Chair for a working party at the European Network for Paediatric Research at the EMA, and also chairs the Children's Research Industry Group for the National Institute for Health Research's Clinical Research Network.

Previously, Susan worked at Servier in their UK R&D department as Clinical Research Manager covering the cardiovascular therapeutic area, followed by more than six years heading up global vaccine trials for Wyeth/Pfizer where she was a member of the global submission team for Prevenar 13, providing medical leadership for studies in Europe, India, the US and China. She then joined TMC Pharma as Director of Medical Services for 18 months after which she moved to Premier Research as their Senior Director in Paediatrics.

Susan obtained her medical degree from Manchester University and also holds the MRCP (UK) qualification. She is a consultant Pharmaceutical Physician (CCST 2011), a member of the Royal College of Paediatrics and Child Health and a Fellow of the Faculty of Pharmaceutical Medicine. She was a member of the Nuffield Council of Bioethics Working Party on Children and Clinical Research that published their report in May 2015.

Contact us

U.S. Toll Free +1 866 267 4479
U.S. Direct: +1 973 850 7571
Europe and other areas: +44 203 564 4649
Asia Pacific: +65 6602 1245
Website: www.quintiles.com