Methods in Medicine: Infusing Rare Disease Studies with Innovation

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Although all drug development entails high levels of risk and investment, this is especially true of ultra rare diseases. Today there are between 5,000 and 7,000 distinct rare diseases and each needs to be approached by drawing on the commonalities of these diseases.

Permissive science, innovative trial methodology, evolving regulatory sentiments and increasingly sophisticated commercialization are prototypically present in orphan disease drug development.

The environment for launching a successful rare disease clinical trial is complex, but with a team of cross-functional experts from medical and scientific affairs, disease management specialists, biostatisticians, medical writing and others, these global regulatory experts can leverage their knowledge in different regulatory pathways. Each of these experts has a singularly unique perspective regarding the framework of healthcare as they see it. And they have unique investments in the efforts around drug discovery, development and commercialization. By using a team approach to navigate the regulatory hurdles, these experts can add significant value in successfully managing the complexities of rare or ultra rare studies.

Managing Regulatory Risks

There are increased regulatory risks in clinical trials being conducted today because of a lack of approval therapies for a given ultra rare disease and a deficiency of well-established road maps for regulation approval. Added to this are the increased risks and costs of manufacturing ultra orphan drugs, as often these are complex biologics.

Despite these issues, regulatory issues can be managed by early identification of organizational methodological, financial, quality, and safety challenges. Having agreed upon the protocol design and the clinical development plan also significantly increases the chances of having a favorable regulatory assessment.

Increase costs and risks of manufacturing are also present in clinical trial start-ups. These can be addressed through successful filing of orphan drug designation applications with the European Medicines Agency (EMA) and the Food and Drug Administration (FDA).

Crunching the Data

In orphan drug development, the evaluation of the environment is critical. This evaluation starts with a full detailed assessment of the incidents and prevalence of data. The competitive environment with other clinical trials and standards of care throughout the globe should also be evaluated.

It's important to note that multiple factors impact research and development efforts in orphan drug development and can result in conflicting and diverse data outcomes. Acknowledging these outcomes is part of a prototypical registration process and part of the current environment in the orphan disease space.

So the emphasis on research and development efforts should be placed on data generation and evaluation, not model development. This evaluation is equally as important as the design of study. Additionally, it's important that the sponsor and CRO have data-driven analysts available for evaluations. Each clinical trial group needs to have analysts that know how to analyze and evaluate data and make it directional.

Generic data needs to resonate in a very diverse group of stakeholders to assure three things. First, the data needs to highlight appropriate medical use. Secondly, the data should allow for unencumbered patient access to therapeutics. And third, the data should describe the potential impact of the therapy on a system of care.

But barriers need to be addressed with clinical trial data that speaks beyond the efficacies and safety of the product to the value of the product. The diverse coverage mechanisms in place, including private plans, Medicare and Medicaid all have different data needs. Clinical trial data needs to influence policy and influence how commercial and governmental insurance plans view the clinical data generated.

Orchestrate Patient Outreach

In clinical trial start-ups aimed at orphan drug discovery, one of the biggest challenges to overcome is the need to identify sufficient numbers of patients to participate in the trial. While there can be many control mechanisms in place that will dictate patient access, the study needs to be very tailored to the patient and to the site population.

Patients and caregivers are typically quite educated on their disease, and the bond between patient and physician can be quite strong. There must be strong engagement from CROs, sponsors and investigators to ensure a successful patient recruitment. This engagement should begin at the earliest time to ensure that all feel engaged with patients in developing protocols.

In identifying appropriate patients, registries in Europe support comparable and coherent databases of patients suffering from rare diseases. Patients can also be identified through the contact of international rare disease research consortiums, such as Eurodisk and the National Center for Advancing Translational Sciences. These organizations work to foster international collaboration through preclinical and clinical research in rare diseases.

Where rare diseases are rare, rare disease patients are quite numerous. Many can be found and enrolled in rare disease clinical trials by approaching patient advocacy groups. CROs, sponsors and investigators all need to engage with patients through these patient advocacy groups. It's important to reach out to these groups, especially if there is a

protocol that is in the process of starting because getting buy-in on the design of the protocol is important.

Most advocacy groups are often started by caregivers who have bonded during treatment or are started by the children of the patient under their care. Patient advocacy groups will usually expand to include physicians and key opinion leaders (KOLs) in each of the indications. By engaging and talking to each of these advocacy groups, investigators can learn what is important for each disease, what affects patients and what is important to the caregivers that surround these patients. In many cases they're smarter about rare diseases and investigators need to take that into account in speaking with these groups. It's important that investigators engage the people that make up patient advocacy groups as equals.

Physicians also play a key role in clinical trial enrollment. There has been reluctance of local doctors to enroll patients to receive treatment at sites outside of their jurisdiction. The largest draw for getting physicians to buy into a clinical trial and enrolling local patients is offering a rare disease compound that is both novel and has promise to help their patients. If the compound is attractive, physicians can drive that message. Subsequently, patients will share the motivations and participate in the trial.

Parallel to enrolling patients, clinical trial investigators need to take patient and caregiver experience into account in the initial design of the study. In many instances, ultra rare disease trial sites are research naïve. Investigators need to go where the patients are, which may or may not be a geographical concentration. Sites need to be identified quickly to ensure that the right patients and sites are being reached. Investigators and trial sponsors are not recruiting a patient to the study as much as putting a network around that patient.

The transportation of patients for treatment, particularly cross-border patient transfer strategies, must also be taken into consideration. The most obvious consideration is the financial aspect relating to the cost of travel, which includes the arrangement of necessary visas that must be met for patients, caregivers and next of kin. Accommodation costs and the paying of onsite translators most also be included.

Ethical considerations of transferring patients also should be taken into account in light of locally existing treatment options. And the translation of records, protection compliance requirements need to be considered.

In some cases the patient will spend two hours getting back and forth to a site up to 12 times a year to participate in these studies. Anything that the study team, the CRO, and the sponsor can do to remove the burden off of the patient and the caregiver will benefit retention and increase outcomes. Of note, patients with rare diseases and their families are willing to be inconvenienced more than typical study patients. However, it's vital that we provide service to minimize inconvenience and also ensure that there is small to no cost to the family for study participation, especially for those that travel from one region to another.

Develop Strong Methodologies
There are currently two routes for gaining clinical trial authorizations in Europe. The first is the National Submission route, which requires national authorization of the orphan drug trial in individual member states. The second is the PHP or centralized route, where applications are made directly to the European Medicines Agency (EMA) with the goal of gaining approval throughout the European Union. This is soon to be replaced with a new directive in 2018.

The PHP, or centralized procedure is recommended. This procedure involves a series of stages beginning first with centralized applications for all member states to review. Once approved the application should be followed up with local and national applications to each member state concerned. The benefits of this submission and review of the protocol and technical dossier can be made well in advance of potential investigative and even patient investigation. And through this submission route, it can be quickly determined which national member states in Europe are likely to reject the study involving patient transfer to the U.S., and which countries will be open to review.

Once the HP level is attained, the application will need to be made to the individual member states, including ethics committees, before the patients can be enrolled in the study. This option provides the opportunity for early indication of agency sentiment with regard to the trial design prior to incurring country specific regulatory submission, preparation and translation costs. And more importantly, it provides the opportunity to explore the concept of conditional approval based on the provision of site-specific details at the time patients are identified.

Outline Methodological Steps
There are key components that need to be taken into account when evaluating and implementing rare disease studies. Specifically, CROs and investigators should review specifications regarding cultural, site and patient considerations for conducting rare disease trials.

As there are a limited number of rare disease experts some evaluators may not have the optimal understanding of the disease methodology used. Therefore, pre-IMBD meetings or scientific advice to discuss the methodological safety reporting, quality reporting, and administration and regulatory issues are in order to facilitate smooth approval of the research trials. Engaging in discussions with the FDA with regards to an accelerated new drug application (NDA) approval, agreeing on the clinical development plan and filing an IMD will greatly assist in addressing all of the main challenges.

CROs are great operational partners, but sponsors that develop medications for rare diseases are typically very passionate about the disease and their compounds. Therefore, they play a key role in investigator engagement. CROs can help facilitate these interactions, but early, direct and frequent site contact between investigators and sponsors is essential. CROs and the sponsor need to work with the site to bring them along on good clinical practices and educate the staff as to how to conduct effective research.

To achieve this, sites need to be research capable. Since CROs and sponsors are going where patients are, they may counter sites that are industry research naïve. So choices need to be made. One choice is to make the site research equipped by providing the staff, resources and training that they need. This will take time and effort from the CRO and the sponsor and also will introduce some risk in conducting a trial with the new site. Alternatively services can be provided to transport patients to the closest research facility.

Attributes also need to be applied to the staff to help ensure success. This starts with engagement at the entire team level with those patient advocacy groups. And it's important that each member of the staff receive therapeutic area training. In this way they can receive information regarding the disease biology, the specifics of the intervention and the design of the study that is being applied. It is important to arm the team with enough information to be a good colleague, so they know which questions to ask at the site level and during the study design process.

Ideally, clinical research associates would have previous experience in rare and orphan diseases. And whenever possible, it's beneficial to assign staff that have bachelor of nursing degrees, or are registered nurses or internal physicians. Even at the project manager level, it's beneficial if the project manager or director can come from a scientific background and are therapeutically aligned within the disease area that is being studied. In this way the staff is educated, engaged with the study and should find it intellectually stimulating.

Engaging Key Opinion Leaders (KOLs) is usually a good idea for many clinical trials, but with rare diseases, it's absolutely essential. More often than not, rare disease physicians and investigators know each other globally, and if the most influential KOLs are not proactively engaged, the study will fail. Also a determination needs to be made of the cultural relationship between these KOLs and the networks. Is it a network that works closely together and collaborates, or there are some that are based more on competition between the investigators? The culture also needs to be tapped to ensure effective outreach.

Other methodological steps need to be considered:
Education and support. There needs to be sufficient and significant physician education and patient support in post marketing research once an ultra orphan therapy is approved.

Physician referral. Physician referral programs in rare diseases are typically more accepted in the cutting-edge treatment of rare disease clinical trials. These physicians can play a key role in not only locating appropriate patients for rare drug trials, but they also can keep patients actively involved throughout the trial.

Operations. Operations need to be closely integrated with the study design. Integration needs to be extended to support the patient caregiver when it can benefit the participants.

Translations. Having access to high quality global translation vendors is key to facilitating a rapid submission in response to agency questions.

Insurance. Partnering with a global insurance broker and discussing the trials features as early as possible is recommended, as obtaining insurance coverage creates another level of complexity in drug trials.

Publication. A publication strategy that complements drug trial approval is important to enhance physician awareness, influence various types of payers and escalate product adoption and influence. Publications should be high quality and peer-reviewed. Individuals studying and writing articles regarding rare diseases are usually quite passionate and will be more likely to carry the message of drug trial approval.

Gratitude. Recently some sponsors have started to thank clinical trial participants at the end of their commercials for marketed drugs. This is one small step in raising awareness and it should continue to grow.

Seek an Integrated Approach

While today's initiation of rare drug clinical trials is more challenging and complex than ever before, the proper planning and approach will not only make a clinical start-up easier, but also more successful.

CROs, sponsors and investigators all need to work together from the start in building rapport and collegiality to create a portfolio of observational studies for typical rare disease interventional trials. These studies should aim to inform patients, family members and physicians and should also be designed to enable responsible decision making for those in the community who play a key role in influencing patient access.