WORLDWIDE CLINICAL TRIALS

WHITE PAPER

FEASIBILITY IN UNCOMMON POPULATIONS

BALANCING AND IMPROVING THE INTERESTS OF PATIENTS, SITES, AND SPONSORS

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How do feasibility determinations for interventional studies in pharmaceutical research differ when addressing rare diseases? The process has changed radically over the last few decades as incorporating the perspectives of many different stakeholders in trial design and operations has become more important. Protocol development addressing rare disorders with significantly unmet clinical needs is no longer the isolated remit of those sponsoring the trial. Design now begins with the patient and extends to incorporate the input of the patient's extended support group as well as contributions from multiple healthcare providers. Design also accommodates ongoing changes in healthcare delivery as well as the evolving regulatory sentiments that enable these trials.

Today, feasibility starts during protocol design: innovative study designs and end points, novel treatment options, and expanded regulatory options are all explored at a very early stage. The timing and the propriety of expanded access programs for patients are considered as part of a process that attempts to maximize access to the active treatment and minimize exposure to the control.[1,2] The potential for accelerated approval pathways, fast track designations, and breakthrough therapy designations when data are appropriately supportive add additional dimensions for review when considering strategic program options.[3]

This paper will examine ways in which the approach to feasibility in rare, geographically dispersed populations has evolved, with particular attention to the perspectives of those stakeholders responsible for facilitating trial design and operations. How the research and development process approached that goal previously, modified the process recently, and continues to examine new directions for innovative solutions in the future is a focus of review.

CONNECTING RARE DISEASE PATIENTS WITH STUDIES

In the realm of rare disease research, one of the chief rarities is insight: Who *has* the disease in question? Are individuals cognizant of the diagnosis? And can a pathway for patient identification accrual be identified pragmatically? As the first step in the pathway toward a clinical trial, it is critical to consider how researchers will reach these individuals.

Dealing with the known is one thing

When a disease pathway (i.e., the sequence of encounters that first identified a patient's suspected disorder) is known, some of these questions can be answered through traditional feasibility techniques. Practitioners may be identified through databases or may be known to physicians and other healthcare providers who have collaborated for clinical care with the specific indication. Outreach through individual centers can snowball, leading both to a list of potentially suitable trial sites and ultimately eligible patients accommodating the geographic distribution of potential participants.

For example, if an indication involves a pediatric heritable disease, it would be important to consider countries and states that routinely conduct newborn rare disease screenings. In the US, approximately 4 million babies are screened for heritable diseases each year. Of those, more than 12 thousand babies are identified with "a disorder that, left undiagnosed and untreated, would cause severe developmental disability or death."[4] According to the National Organization of Rare Disease Disorders (NORD), states that conduct newborn screenings are more likely to help parents connect with medical experts and support groups.[5]

Patient insight networks (PINs) can also help identify prospective participants when the disease pathway is known. Patients can then be directed to centers of excellence for further care. National and international groups established to advocate on behalf of patients with a particular condition also

can play a significant role here. Indeed, rare disease patient groups increasingly influence discovery research by providing the initial investment to both academic and commercial organizations, characterizing pathophysiological processes, and identifying potential targets. Individuals within these organizations also share trial design and program strategy and ultimately may influence regulatory policy.

Dealing with the unknown is something else

But how can a sponsor or clinical research organization (CRO) identify and accrue trial participants and suitable sites when a disease pathway itself – from initial suspicion to confirmed diagnosis – remains unknown? This challenge looms large in rare disease research. Clusters of signs and symptoms do not constitute a diagnosis, so patients afflicted by some rare diseases often remain improperly diagnosed (or entirely undiagnosed) for many years.[6,7] The algorithmic mining of data from health research networks may identify patterns of care and, subsequently, physicians whose patients might be suitable candidates. However, the likelihood of such data mining delivering deep insights into the *experience* of the illness (as opposed to the presence of a diagnosis) is unlikely. The analytical tools that might yield those insights are in their infancy. For this reason, personal outreach to patients and family members is considered essential.

STRATEGIES FOR RARE DISEASE PATIENT IDENTIFICATION

PATHWAY IS KNOWN

- Snowball technique
  - Refer to literature and experience for KOLs in indication and also refers colleagues treating disease
- Hub and Spoke
  - KOL at university hospital has referral networks that can support recruitment
- Registries and advocacy group involvement
- Patient insight networks - access to registry information
- Prescreening protocol
- Family histories

PATHWAY IS UNKNOWN

- Cluster of signs and symptoms not equal to diagnosis, patient not diagnosed
- In isolation, signs and symptoms mean nothing
- Other vendor services are available:
  - Access to large database of information: DOD, Medicare services, etc.
  - Aggregate data using algorithm determined by medical team (data mining)
  - Allows for patient outreach through physician

THE EVOLVING IDEA OF SITE SITUATION

The identification of suitable trial participants is only the first feasibility hurdle. Once sponsors and trial designers have an idea of where participants are located geographically, the question arises of where best to establish trial centers – both in terms of center topology and geographical location. The answers to this question will depend on the nature of therapy, route of administration, the nature of the data to be collected, and the availability of sufficiently trained personnel and accessible facilities. Traditionally, study centers acted as the "hub" where in-person, on-site study visits were conducted on a regular basis. Rare disease study patients traveled – sometimes long distances – to medical centers for study-mandated in-clinic visits that frequently condensed a high number of procedures into a brief period of time. These visits were also often scheduled with a frequency that patients and their families found difficult to accommodate. These twin issues of "visit density" (the number and complexity of in-clinic assessments) and "visit frequency" (mandatory in-clinic measures within a longitudinal study) posed significant burdens on patients and families throughout the course of a trial, frequently affected the quality of the data, and emerged as a major consideration for study designers over time. It became clear to researchers and sponsors that factoring clinical care and patient burden into the earliest phases of trial design was important, particularly for advanced therapy medicinal products in which patient tolerance and safety as well as efficacy became equally dominant themes.

Now, patient needs, limitations, and operational challenges are routinely incorporated into protocol design and country/site feasibility studies. Sponsors have acknowledged that *understanding* the pathophysiology of a rare disease provides only a foundation to build upon. Successfully addressing relevant hypotheses through observational or interventional research depends upon operationalizing an understanding of the unique needs of those with the disease and their care partners. Currently, subject matter experts in clinical trial methodology and operations routinely consult with patient and support groups early in the protocol design process to ensure that visit frequency, assessments, and the overall patient burden remains consistent with the objectives of the trial. They continue to interact with patient advocates and support groups throughout the drug development process to gain a better appreciation for the experience of the illness, which informs and may modify the overall trial strategy.

These interactions are now seen as foundational to a successful trial and clinical development program. This approach lends itself to learning and adaptation through time, too, as trial designers and subject matter experts in study feasibility can conduct a focus group or survey in partnership with an advocacy group and investigative sites to continuously improve feasibility and protocol implementation at study centers.

IS ATTENDANCE AT THE CLINIC NECESSARY?

When identifying patients to participate in a study, it is important to consider their location in terms of both *their* access to a research site as well as the *site's* characteristics and capabilities in the areas of clinical care and research. Data indicates that approximately 70% of potential participants live more than two hours away from a study center.[8] Increasingly, trial designers are finding ways to combine a variety of assessment options – including in-clinic or at-home procedures – in ways that meet protocol requirements while improving the study

experience for patients and sites. Such options have included:

- Home health visits by study nurses to administer treatments and procedures. With specially tailored training programs, home healthcare providers can enhance both surveillance for safety and the acquisition of clinical data. One author notes, "this ease of participation directly increases patient recruitment by 60% or more and typically maintains retention at over 95%."[9] This metric is likely affected by the indication, the intervention, and the complexity of study-related procedures.
- Virtual visits with the study doctor using video or phone.[10]
- Digital technology and wearables programmed to upload patient data remotely. This approach can provide a more environmentally relevant mosaic of data across time, not just a cross-sectional assessment of information based upon isolated observations taken during clinic visits.[10,11]

The risk of fragmentation in a trial process that mixes at-home, in-clinic, and/or telemedicine-based interactions looms as a dominant factor in considering the qualitative aspects of data acquisition. It needs to be addressed, since such fragmentation could, in theory, introduce changes in both the detail and perhaps the quality of the data gathered. Several scenarios suffice to illustrate this potential:

- Lack of in-clinic patient contact could compromise the quality of clinical assessments if the accuracy of those assessments depends on the observations of a highly experienced healthcare provider with knowledge of both the disease and the particular presentation of a given patient. Although, the increasing use of telemedicine suggests an emerging opportunity for this technology may exist for trial conduct.
- Studies with frequent, richly detailed site visits versus studies that emphasize home visits theoretically may yield differences in generalizability of results, even though study conduct at each location may be completely valid.[12]
- Within a study, a shift from in-clinic to at-home collection of measurements for the same assessment might impact the overall results.[13]

In response to these and similar risks, designers have learned to pay particular attention to the credentialing of assessors, training, and surveillance mechanisms that follow study initiation. The exigencies of the coronavirus pandemic have forced sponsors and trial designers alike to embrace accommodations in order to execute trials in a manner that remains safe, productive, and valid.[14]

THE RISK OF SACRIFICING "UNSPOKEN" MEDICAL NEEDS

The caveat attached to these feasibility options is straightforward: *consider them when they make sense for the study patient*. Some patients may be unable to tolerate digital technology or wearables. Or, the communications infrastructure in certain regions may be too unreliable to ensure consistent digital data uploads. Even in the absence of such negating factors, existing psychosocial support systems may be strongly associated with a healthcare provider, which could, counterintuitively, decrease enthusiasm for a home-based study among patients and caregivers who would prefer to travel to a site. There is also evidence suggesting that some patients prefer to travel to an external site for care because it helps facilitate an experience of camaraderie among trial participants and medical staff, which

provides a unifying fabric for study participation.[10] Trial techniques that cause clinical care to intrude into the home, for such patients, may not be universally endorsed. A focus group can be helpful in making these determinations during the protocol design phase.

BALANCING AND IMPROVING THE INTERESTS OF PATIENTS, SITES, AND SPONSORS

It used to be that the needs of patients with rare disease were accommodated only when they were discerned within the context of a study. The fact that existing protocols frequently are retrofitted after the fact to accommodate novel situations arising in rare disease studies provides some attestation to the inadequacy of traditional feasibility processes.

Today, considerations acknowledging the nuances of rare diseases are built into protocol design and site selection from the earliest stages. Effective feasibility assessment involves asking the right questions of sites, and for rare disease studies, those questions can differ greatly from those one might ask of a site for a trial involving a more traditional condition. To balance the integrity of study data, study patient burden, and site capabilities, for example, trial designers, subject matter experts, and trial operations personnel must consider and prioritize rare disease study procedures in ways that are consistent with the umbrella of hypotheses that are usually generated. The timing, order, and logistics of visit procedures should quickly identify safety issues, limit physical and emotional demands on study patients, and make best use of study center personnel attention.

Indeed, trial designers need to apply these patient considerations when conducting feasibility outreach to sites. Large institutions and children's hospitals are usually well equipped to accommodate rare disease studies and patients. Multiple teams within these institutions are frequently involved in care and can contribute insights informing study design and trial operations.

SUMMARY

Ultimately, every rare disease is different, and every person with a rare disease is unique. The spectrum of clinical phenotypes that can exist, even with ultra-orphan indications, place a demand on sponsors and study methodologies to keep the heterogeneity of clinical presentation and the needs of the patients in mind – not only in terms of protocol design but also in all elements related to its implementation. Study feasibility efforts benefit most when designers continuously apply lessons learned about how patients manage in their day-to-day lives, particularly when it comes to patient perceptions about novel technologies or the expansion of research procedures that may intrude upon their home environments. They improve when sponsors and trial designers listen to and interact with patient advocacy experts. Such interactions lead to operational strategies that can simultaneously enhance the experience of the patients and the value of the data collected.

Traditional approaches to feasibility focused on patient accrual as a means to an end. Innovative methods, while retaining the objective of patient accrual, place that objective in a broader context that appreciates the experience of the illness, the patient perspective, and the need to accommodate research and development activities within the context of clinical care.

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