Worldwide Clinical Trials

Incorporating the Patient's Voice

Informing Clinical Methodology in Orphan Disease Research

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Introduction:

The heterogeneous manner in which many orphan diseases present among patients poses unique challenges when it comes to clinical trial design. Defining what constitutes a meaningful change is particularly complex when the disease manifests differently in each individual. It is crucial to appreciate the concept of meaningful change from the patient's perspective and, if appropriate, include the caregiver's perspective. This understanding is vital in the short term for drug development and trial design and, in the long term, for ensuring drug access and adoption. This paper examines methods for gaining insight into patient and caregiver perspectives and considers the strengths and weaknesses of these methods.

The goal of clinical research is to provide safe and effective disease treatments that lead to relevant and meaningful improvements in a patient's functioning and quality of life. While there are many challenges inherent to clinical development in an orphan indication, the heterogeneous manner in which many orphan diseases present among patients contributes significantly to the challenge of clinical study design. For instance, in one patient, the salient character of a disease may be found in limitations in functional mobility at a level of severity that significantly impairs activities of daily living. In another patient, the salient characteristic of the same disease might be fatigue or pain or inattentiveness arising from the pain that is unpredictable and prevents the individual from being able to maintain employment or attend school. Creating and capturing a uniform construct across patients with significant heterogeneity in presentation, particularly in studies with a small sample size, is a recognized challenge. The underlying pathophysiological basis of the disease is the same, but the "illness" — how the disease affects each patient — may differ. Thus, designing a clinical study that will detect meaningful changes within a patient population requires an appreciation of what actually constitutes a meaningful change for patients and/or caregivers, and it emphasizes the potentially seminal contribution of patients and families in the creation and operational implementation of study assessments.

The most informative way to appreciate patient-specific differences in disease manifestation is through direct patient engagement. What vocabulary do patients use to describe or characterize their symptoms and experiences? Which disease characteristics do patients and caregivers experience as having the most significant impact on physical and emotional functioning or quality of life? An understanding of the patient's experience can help a drug developer improve its ability to communicate with patients and caregivers about the disease (using terms that will resonate). Patient and family engagement can also facilitate the drug development process and help shape its strategic implementation. Strategic partners — including regulators, investigative sites, and clinical care coordinators — can thus construct clinical trials in ways that facilitate capturing critical data about the patients' experience of a disease and the effects of the investigational product (IP) being developed.

Figure 1: An understanding of the patient's experience can help a drug developer improve its ability to assess meaningful improvements in a patient's quality of life.

A Portfolio of Approaches

There exist many ways to capture the patient's voice, but four specific techniques have repeatedly proven valuable to clinical trial developers:

- Literature-based surveys
- Web-based surveys
- Exit interviews
- Observational studies

While each of these techniques can provide insights into the patient's voice that are useful for any clinical trial, they each offer specific advantages in scenarios where a study targets a rare or orphan disease. Recent experiences with implementation of these approaches provides the impetus for this review.

Literature-Based Surveys

Literature-based surveys can provide useful insights into the patient's voice in orphan disease scenarios where there exists an abundance of literature about the disease. One recent case where a review of the published data was leveraged successfully was in advance of a potentially pivotal Phase 3 trial involving an orphan disease whose heterogeneous presentation suggested multiple domains of importance. There was disagreement among stakeholders (the sponsor, clinicians, and advocacy group members) about which of these domains was of primary importance, and a composite assessment was under consideration. Thus, it became important to identify the most relevant, common, and frequently voiced patient concerns so that primary clinical measures and endpoints could be determined and agreed upon by the stakeholders and the regulators who would be reviewing the study data.

In this instance, a considerable body of work existed within the literature about the disease, including recently published results from contemporaneous patient and caregiver surveys. Qualitative analysis of the literature for insights into the patient's voice yielded key information, such as the primary domain of interest and measures that could be employed, from which the primary, secondary and exploratory endpoints were identified for inclusion in the Phase 3 trial. Conversations with key opinion leaders (KOLs) validated the findings from the qualitative literature analysis, and ultimately the proposed study design was accepted by stakeholders and regulators.

Adopting the results from this targeted literature review enabled trial designers to avoid attempting to embrace an unwieldy number of domains, measures, and endpoints, the pursuit of which could have jeopardized data acquisition and created challenges in the statistical analysis that would not have been easily remediated. By focusing on a single domain of import that was well documented in the literature, trial designers were able to modify the trial through eligibility criteria, stratification factors, sample size, and methods of analysis in a manner that would streamline trial execution while enhancing trial sensitivity. Because these proposals could be justified by the data presented in the literature, the study design was approved by regulators, participating sites, and most importantly, could be readily endorsed by patients and caregivers.

Figure 2: Literature-based surveys are appropriate for orphan indications where considerable prior art exists.

Web-Based Patient Surveys

A web-based survey provides a way to present patients or their caregivers with a focused set of questions that may be answered from anywhere the web can be accessed. Participants can review and respond to questions early in the development process or even during discovery, which ultimately enables trialists to capture critical input about patient experiences before a study. This is particularly useful in situations where the existing literature does not provide much (or any) information about patient experiences.

Such a survey was recently used to capture data that ultimately helped shape inclusion/exclusion criteria for a planned study, identified a suite of relevant outcome measures, and assessed the willingness and ability of patients to complete certain types of assessments and procedures. In this instance, an advocacy group external to the planned trial conducted the confidential and blinded survey. However, such surveys can also be conducted by the clinical research organization (CRO) managing the trial or a sponsor with a long-term investment for a strategic program in a given indication.

The web survey included questions with response options utilizing check boxes, Likert-scale responses, or free-text responses from which data was later extracted. It was designed to assess important disease symptoms, which allowed trialists to reprioritize the domains of import and attendant assessments. For example, one domain of disability that initially had not been weighted heavily (based on the literature review) was elevated in importance based on the more comprehensive review of current family and patient experiences returned by the survey. The incorporation of a free-text option in the web survey also led to the elicitation of concepts not previously considered.

Figure 3: Web-based surveys enable trialists to assess important disease symptoms and the feasibility of assessments.

The patient and caregiver response to the web survey also provided a way to assess the feasibility and acceptability of conducting other assessments over the course of the study. It also provided insight into patients' and caregivers' understanding of the risks associated with certain specialized procedures. As was the case in this instance, these considerations are critically important when a study involves a special population (such as a pediatric population or a population with cognitive challenges) for whom some assessments would be inappropriate or when a study involves specialized procedures that may not be feasible in certain populations (such as lumbar punctures). Results of the survey also highlighted the need to develop patient- and caregiver-facing educational material regarding certain types of specialized procedures.

Exit Interviews

A third way to capture the patient's voice involves an exit interview. Such interviews typically involve a structured or semi-structured qualitative interview with a patient or caregiver that is conducted one-on-one by a trained third-party interviewer (i.e., someone not otherwise involved with study conduct) at the end of a study. This technique provides a way to gain insight from the perspectives of patients, caregivers, and/or family members into the *experience* of the study treatment in the context of the illness. Early in the clinical development program, these interviews can be utilized to elicit information about the interviewee's experience of the disease, including symptoms and impacts of greatest importance, as well as obtain feedback on the relevance of outcome measures that were used in the study or candidate measures in consideration for future trials.

Exit interviews must be performed in a manner that builds participant rapport while avoiding interviewer bias. Questions must be fully vetted by all relevant stakeholders prior to the interview, and treatment group assignment should not be a relevant domain for consideration. Additionally, the interview approach and flexibility within that approach should be prospectively considered, especially when interviewing special populations such as pediatric patients or patients with cognitive or communication challenges. For instance, the use of age-appropriate vocabulary or an interview setting that may mitigate potential anxiety-inducing triggers are two elements to consider.[2] At study conclusion and following database lock, an appropriate analytic approach to these qualitative and quantitative data could provide indirect support for product attributes complementary to the traditional hierarchical approach to primary, secondary and exploratory measures.

Feedback regarding the impact of study treatment on the patient or caregiver experience of an illness is critical when endpoint change thresholds have inadequate precedence. This latter concept has frequently proved to be the Achilles' heel of multi-domain responder indices (MDRI) in that threshold levels for meaningful response can be elusive in the absence of a comprehensive modified Delphi setting, even if individual parameters for a composite response can be advanced. A change in one domain may be statistically significant, but it may not represent a meaningful change if the patient's or caregiver's *experience* of the disease remains the same.[3] Exit interviews can help identify the *qualitative* changes that are important to patients and their caregivers, and from those insights, developers, trial designers, and others can adjust their expectations accordingly.

Exit interviews were recently integrated into an early phase safety and pharmacokinetic study to elicit information directly from adult patients living with a rare disease. In this instance, because there was limited data to inform a clinical outcome assessment (COA) strategy and no disease-specific measures considered appropriate for the target indication, exit interviews offered an attractive method for collecting patient experience data. The study did not collect any COAs during the treatment period but included a combined concept elicitation and cognitive debriefing interview at the end of the study that sought input from the affected individuals about their disease and their impressions of assessments that might be used to characterize the change in their disease with treatment. With this objective in mind, the interview was structured to draw information about participants' experience living with the condition, learn about changes in symptoms that would be most meaningful to them, and gather their perspectives on the relevance of sample outcome measures, their experiences participating in the safety study, and their observations from taking the study treatment.

The qualitative feedback collected during these exit interviews confirmed that these individuals experienced a range of debilitating symptoms related to their condition. Moreover, the mix of symptoms they experienced varied substantially from patient to patient. Nearly every participant confirmed that the episodic symptoms they experienced were so severe that *any* change resulting from treatment — positive or negative — would be meaningful and important. The interview data also provided a rich set of supporting evidence to develop a diary to characterize change in frequency and severity of patients' episodes in future interventional trials rather than targeting the inclusion of questionnaires focused on a narrow set of symptoms that may be meaningful only to a subset of patients. Additionally, patient responses to a set of exit interview questions about COAs used in similar indications identified an existing measure that could potentially be adapted for use in the target population and that might provide another avenue for characterizing treatment benefit.

In this case, incorporating exit interviews into the early safety study was an efficient and cost-effective method of collecting qualitative data directly from patients. That data can then be used to inform future trial design and strategy.

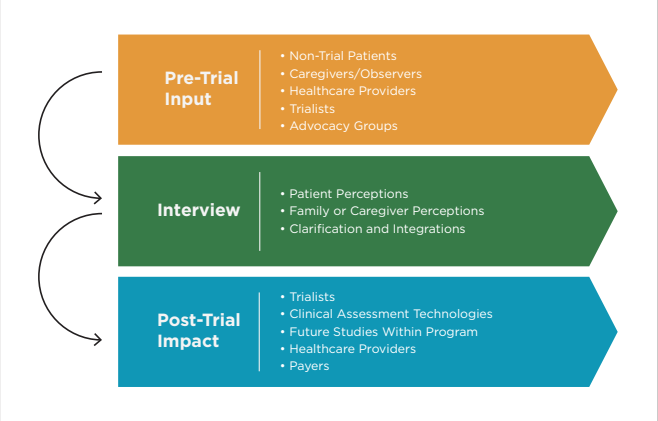

Figure 4: Exit interviews can help identify the qualitative changes that are significant to the patient and their caregivers, and from those insights developers, trial designers, and others can adjust their expectations accordingly. Adapted from Contesse et al.[1]

Stand-Alone Observational Studies

Stand-alone observational studies — those studies that stand apart from an interventional trial — have been used to provide the most direct access to the patient's voice and an understanding of a patient's experience of a disease. Like the exit interview, a stand-alone observational study typically involves a structured or semi-structured interview conducted by a trained third-party interviewer, and it often takes place in advance of a formal clinical trial. Observational studies

can enjoy the many attributes of an interventional clinical trial, including the use of standard as well as disease-specific bespoke assessments and a visit structure that is compatible with data acquisition. This also includes hybrid clinical trials with a mix of in-clinic or decentralized features, methods of credentialing and training assessors, and a program that assures compliance for quality control by all participants. A full panoply of analytic techniques suitable for observational studies provides context for interpretation. An advocacy group might suggest patients (and/or caregivers) who can participate in the observational study, and the interview would be designed to help identify the symptoms, domains, and endpoints that are meaningful to patients and caregivers who are experiencing the disease. At the same time, these measures could be prospectively correlated with other clinician-, observer-, and performance-based measures, or patient reported outcomes.[4]

In a rare or ultra-rare disease scenario — where there may be much uncertainty or disagreement among stakeholders, KOLs, and regulators about which domains, measurements, and clinical endpoints are most important — a stand-alone observational study is the "classic" way to help parties gain a better understanding of the patient's experience of the disease and how the disease and its symptoms affect the patient's life. This kind of study could, for instance, provide the foundational insights that identify the types of articles that might later be used in a literature-based survey (as discussed above).

While there are distinct high-level benefits to using a stand-alone observational study to foster consensus among stakeholders, KOLs, and other engaged parties, there are both practical benefits and encumbrances that can arise from this exercise. As the patients' voices shed light on the importance of distinct disease domains, endpoints, and measurements, it becomes possible to develop a list of frequently mentioned concepts that can inform subsequent clinical trials. Trial designers can determine whether there are suitable COAs that can be used in a clinical trial setting to monitor and assess changes relevant to these concepts. They can also perform a pre-trial gap analysis to determine if any of the frequently mentioned concepts remain *unmonitored* by the identified set of COAs and then suggest further COAs to fill in the gaps as necessary. The major encumbrances of this approach involve resource allocation, a delay in implementation of a potential interventional study (always unwelcome, but particularly so for diseases with substantive unmet need), and the possibility that eligibility criteria for the interventional study (age limitations, for example) will preclude participation of some patients who had already volunteered for observational research — a concept occasionally referred to as "falling out of the eligibility window."

In some countries, a stand-alone observational study intended to test the viability of procedures that might later be used in a clinical trial may be subjected to the same regulatory review process as an interventional study, as it may not reflect the local standard of care. If trial designers are unsure whether a mobility procedure might be customarily employed in a clinical trial setting, for example, a stand-alone observational study can provide an opportunity to make a pre-trial determination. Note that not all countries allow the testing of procedures that are not considered standards of care, and the inclusion of such tests would need to be approved by the local ethics committee before they could be evaluated in an observational setting.

Practical Considerations

Any of the methodologies described above will take several months to complete. Study designers should plan to spend at least three months identifying assessments and writing the protocols to support a planned study. Diseases for which a body of literature exists may require even more time, as there is more

Figure 5: A stand-alone observational study can yield insights that can help steer the direction of future studies.

material that may provide insight into the patients' experiences. Similarly, diseases for which there is considerable disagreement among stakeholders, KOLs, and others about which are the most important domains, measurements, and endpoints may require a longer period of time in order to reach consensus about the experiences to be sought in these studies. How long it will take to engage patients and caregivers, obtain input, and analyze responses (assuming that the method of engagement is not solely literature-based) will depend on a number of factors, including the number of patients and caregivers that agree to participate in the study. Study designers should calculate the human resource requirements for engagement of patients and caregivers at an early date to ensure that the team supporting the initiative — including the third-party personnel that may be conducting interviews and web designers that may be needed to create a portal through which patients and caregivers can complete surveys — is sufficient to the task.

Ultimately, an understanding of the patient's experience is crucial to the success of any drug development effort.[5] Listening to the patient's voice is the best way to gain the insights that will help keep development pointed in the right direction.[6-17]

Figure 6: Capturing the patient's voice helps identify those aspects of the disease experience that are most significant for the patient and his or her family. Examples of utilizing the patient's experience to guide outcome and analysis selection can be found in the references.

Summary

A mosaic of techniques can be used to capture the patient's voice in diseases marked by a small patient sample and exceptional heterogeneity in disease presentation. Methods other than the ones described here exist, though not all are well suited to rare and orphan disease scenarios. Both families and advocacy groups are critical to an understanding of the patient's voice, and the techniques described above make it clear how these participants can help amplify the patient's experience in the earliest stages of discovery and development processes.

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