Methods for Selecting and Measuring Endpoints that are Meaningful to Patients in Rare Disease Clinical Development Programs

Margaret Vernon, PhD, Senior Research Scientist and European Director, Outcomes Research;
Kathleen Wyrwich, PhD, Senior Research Leader, Outcomes Research

The number of targeted treatments in the pipeline for rare diseases has nearly tripled compared to a decade ago.[1] The current and exceptional integration of several factors contributes to this rapid growth of treatments and cures in this arena. Genomic intelligence and associated therapeutic methods are ever-increasing, and pharmaceutical corporations, eager to build on this expanding knowledge, are de-emphasizing their former blockbuster model in favor of increased rare disease solutions. In addition, electronic medical records offer improved capabilities for data analytic methods to find specific rare disease needles in large database haystacks. This, in turn, improves opportunities for greater understanding of their genomics, biomarkers, symptoms, treatments, and ultimately, outcomes.

Stakeholder groups, including regulators, payers, policy makers, and patients, have demanded patient-centeredness in rare disease drug development programs. Patient-centered outcomes research has been defined as, (research that) "helps people and their caregivers communicate and make informed healthcare decisions, allowing their voices to be heard in assessing the value of healthcare options."[2] More specifically, the Patient-Centered Outcomes Research Institute (PCORI) and the U.S. FDA Center for Drug Evaluation and Research have discussed the importance of evaluating disease manifestations that are *important* to patients in rare disease drug development programs.[3] Furthermore, in a comprehensive review of orphan drugs submitted for health technology assessment (HTA) in Europe, Lyons et al.[4] found that HTA bodies regularly requested data from patient-reported health-related quality of life (HRQL) assessments included in clinical trials; Germany and France emphasized outcomes that would demonstrate clinical relevance of interventions to patients. Key decision makers in both the U.S. and Europe, and elsewhere around the world, are placing emphasis on outcomes *important* to patients in evaluation of orphan drugs.

Thus, patient-centered outcomes, most recently defined as, "those outcomes important to patients' survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in the patients best interests by providers and caregivers when patients cannot report for themselves,"[5,6] are critical for inclusion as endpoints in rare disease drug development programs. However, the methodological challenge in developing outcome measures capable of achieving this definition's intent include: 1) defining endpoint concept(s) that are meaningful to patients, and 2) selecting endpoint concepts and measures of these concepts that are hypothesized to demonstrate a treatment effect, taking into account treatment mechanism of action, patient population included in planned clinical trials, and clinical trial design factors. This article focuses on the first challenge of identifying the endpoint concept(s) that are most meaningful to patients.

A key aspect of enabling optimal patient-centered endpoint strategy for clinical development programs is an early initiation of the necessary background research and endpoint planning, preferably prior to Phase 2 studies. Including the appropriate patient-centered outcomes in Phase 2 studies provides all stakeholders in the rare disease treatment program — patients, their caregivers, investigators, the drug development team, regulators and payers — with first-hand knowledge on the treatment effect measured with these endpoints. Moreover, the learnings from a Phase 2 clinical trial,

in conjunction with regulatory and payers' feedback to the endpoints and results, provides the opportunity for: 1) further improving the endpoints, if fine-tuning is indicated, and 2) a re-prioritization of the endpoints in advance of Phase 3.

A focused literature review of patient- and caregiver-burden and relevant HRQL concepts, as well as an examination of known published reports and recent conference abstracts from other outcomes measures used in prior clinical and observational trials, can provide initial information that is essential throughout the endpoint strategy and selection process. Second, the wisdom from clinicians experienced in treating patients with the specific rare disease can provide invaluable knowledge regarding the relevant disease signs, symptoms, and impacts of these symptoms on patients' lives. Moreover, clinicians with experience in other rare diseases that are very similar to the investigated condition can also offer insights on outcomes that have demonstrated patient-centered benefits in prior clinical trials.

However, in order to determine which improvements in the signs/symptoms or impacts of disease would be most meaningful to patients, patient and/or caregiver engagement is critical and necessary to inform endpoint selection. Yet traditional methods for gathering early patient input, such as focus groups, are very often impossible in rare disease populations due to the nature of rare diseases. By definition, there are few patients with the disease, and there is often a large geographical spread in the scarce number of persons with a specific rare disease. Further, rare diseases often include pediatric populations who either cannot report for themselves or may not reliably report using traditional focus group methods.

Innovative methods to gather patient input regarding meaningful endpoint concepts and measures are essential in rare disease clinical development programs. In early planning, one option for gathering information about important outcomes for patients is to use existing data available directly from patients and patient advocacy groups within a given disease area. Rare disease patient advocacy groups bring passion, enthusiasm, and dedication to assist in achieving this input, and Evidera's frequent opportunities to work with the champions continues to be a remarkable and moving experience. These patient advocates are well connected and tireless in their efforts to seek solutions. At the same time, they are painstakingly cautious in protecting the best interests of all individuals in their organizations.

With this important asset in mind, several other examples of publically available sources are provided below; each can be tailored to many specific rare diseases to provide insight on the patient experience and potentially meaningful endpoints.

- A review of patient discussion boards can provide insights into the important impacts of a disease from patients' perspectives as the patients and their caregivers discuss the day-to-day learnings, new treatments/devices and best ideas for coping with their condition.
- An examination of the reports from patient advocacy groups can provide information regarding endpoint concepts that are important to patients. For example, the Cystic Fibrosis Foundation Patient Registry Report is specifically designed to "identify new health trends, recognize the most effective treatments and design clinical trials for potential therapies."[7] (This registry includes data from 27,000 patients who receive care at accredited centers, and reports are available to researchers.)
- An appraisal of key learnings from some rare disease foundations who have joined forces with parent and patient advocates, clinicians and academic research teams, industry, non-profit organizations and/or government in drug development for a specific rare disease. Having invested in useful research tools, these foundations can greatly assist in understanding key endpoints for inclusion in clinical development programs.

Depending on what type of information is already available in the public domain, additional input from patients will most often be required to understand the full picture of outcomes meaningful to patients within the context of a specific disease area and therapeutic agent. Further, within many rare disease groups, there is a dearth of information regarding appropriate patient-centered outcomes in the literature or public domain. In all cases, gathering input from patients or caregivers themselves is essential.

The first challenge is identifying (enough) individual patients or caregivers/close family members to have confidence in generalizability of endpoint concepts identified as important. It is unlikely that placing general newspaper advertisements or recruiting through several clinical sites will yield enough patients to obtain generalizable results. Examples of innovative methods for identifying patients and gathering input regarding endpoint priorities are provided below.

- We have had success identifying patients to engage in early endpoint planning through partnerships with patient organizations, which often are typically interested in engaging in research that forwards patient-centered outcomes in clinical development programs. Patient associations may email their members study advertisements for opportunities to solicit input; the organization's newsletters, websites, and social networking sites (e.g, Facebook groups) are other venues where advertisements can be placed for study involvement.

- Rare disease scientific conferences often include sessions specifically conducted by patients/caregivers and other sessions designed for patient/caregivers, which assures attendance from patient/caregivers themselves. These conferences provide focused opportunities to recruit patients/caregivers for participation in discussions regarding their disease experiences and priorities for new therapies. These discussions can take place just before, during or immediately after the conference to accommodate patient/caregiver travel plans and their desire to participate in these opportunities to share their input.
- Some rare disease populations, especially those with an approved treatment, have organized disease registries, where patients with a confirmed diagnosis are registered within a database and engage in ongoing research activities. Adding research modules on endpoint priorities, input on patient burden, or other patient-centered outcomes to these databases may be an option to collect information from patients regarding patient-centered outcomes.
- Patients can be identified through on-line patient forums or chat/message boards for participation in research activities.

All of these options may have benefits and drawbacks, and the specific recruitment challenges within a given disease population as well as the research objectives should be taken into account and pros/cons weighed carefully regarding optimal recruitment strategy. Once an avenue for identifying patients to engage in early endpoint planning research has been identified, the next challenge is selecting the best methodologies for gathering input from a diverse and geographically dispersed patient population. Technology-enabled solutions can often address this challenge, and some useful examples are listed below.

- Telephone interviews allow for gathering of semi-structured qualitative patient input without the need for interviewers or patients to travel for interviews.
- Web-based surveys can be used to gather data from patients regarding treatment priorities; a modified Delphi panel technique might be used to gain consensus on endpoint priorities.
- Live on-line patient forums where a moderator posts a question and patients can reply to the question or comment on other responses is an interesting option to gather rich textual data on patient priorities.

In summary, inclusion of patient-centered outcomes in a rare disease drug development program is critical for market access success. Creative and innovative solutions to obtain patient input on treatment priorities are necessary when working in rare diseases due to the very definition of "rare disease." Reaching patients through non-traditional forums and utilizing technology solutions to gather patient input greatly reduces barriers to successfully engaging rare disease patients at this early stage in the drug development process. Including patient advocates and engaging patients throughout a program of drug development can also be enhanced by solutions outlined in this article. Indeed, the scientific challenges for rigorous health outcomes development and validation methods continue to require unconventional approaches and innovative methods because of the important limitations in rare diseases; yet the novel ideas that emerge provide valuable methodological insights for other disease area applications.

For more information, please contact Margaret.Vernon@evidera.com or Kathy.Wyrwich@evidera.com.

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