POLICY ANALYSIS

Focusing on the Patient in Drug Development and Research

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Many terms have been used in discussions of outcomes used in clinical trials to assess treatment benefit for regulatory purposes and in other types of health research that focus on the patient: patient-reported outcomes, patient-based outcomes, patient-important outcomes, patient-focused outcomes and finally patient-centered outcomes. As patient-centered research and regulatory practice come together and center on the patient, the term patient-centered outcomes has come to be used to cover the wide variety of contexts in which outcomes important to patients are used.

Patient-centered outcomes are those outcomes important to patients’ survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients’ best interests by providers and caregivers when patients cannot report for themselves. This definition covers a wide variety of outcomes that can be measured by clinical outcome assessments (COAs), the term the Food and Drug Administration (FDA) uses to include all measures excluding only survival and biomarkers. There are 4 types of COA measures: clinician-reported, patient-reported, observer-reported, and those that measure various aspects of patient performance on specified tasks. Regardless of the type, these outcomes can be considered “patient-centered” when patient or caregiver engagement provides evidence that the outcome is important to patients and establishes a link to survival or how patients feel or function in daily life. Indeed, not all COAs are patient-centered. Many, including many patient-reported outcome measures, have been created by investigators without patient input or involvement, and though these are well-intentioned, without establishing the link to how patients survive, feel or function, they cannot be considered patient-centered.

PATIENT ENGAGEMENT

Thus the first requirement for patient-centered outcomes is the clear involvement of patients with the disease or condition in determining and defining the relevant outcomes before the COA is developed or used. Patient engagement begins as the research questions are being formulated [1]. Studies and research organizations frequently use mixed methods approaches combining in-person venues >

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with structured processes such as Delphi Group web/conference calls that may be combined with Delphi ranking or voting. This is a new science with many challenges and unknowns but experience is rapidly accumulating. Patients experiencing the condition and their caregivers are excellent sources for helping to identify and define the appropriate outcomes that can define treatment benefit in the disease or condition. Along with clinical and measurement experts, patients have the “lived in” experience that informs how the condition and its manifestations are perceived, talked about, and internally evaluated. Patients from all subtypes of the condition under consideration and with all levels of severity should be involved.

Shared decision making is another arena for patient engagement [2]. Shared decision making is an approach that seeks to fully inform patients about the risks and benefits of available treatments and engage them as participants in decisions about the treatments. Use of shared decision making is a way to improve care quality, and payers and providers want evidence that this emerging model of care is cost-effective. Patients who participate in shared decision making often have lower overall medical costs than patients who received the usual level of support2, suggesting some efficiencies in using decision aids. These interventions may reach a broad segment of the population and can be implemented in integrated care settings [3].

Getting patient-centered outcomes into drug development requires patient engagement beginning at the translational research stage (pre-IND) before the initial phases of IND development (Fig. 3). In the Pre-IND phase, patients should be involved in defining the natural history of the disease, the important characteristics of the disease that defines subpopulations, elements of the health care environment that impact outcomes, the burden of symptoms, how daily functioning is impacted, what accommodations are made, and the benefit-risk tradeoffs with the existing treatment alternatives. Patients should be engaged through all phases of drug development to inform clinical trial design, analysis and interpretation. Certainly, patient input is also important to research in the post-approval real-life setting.

The second step in the process of identifying and using patient-centered outcomes is providing a rationale for the selection of the concept of interest that will provide evidence of meaningful treatment benefit. This step involves specifying the logic of selecting the concept and the methods used to define and give meaning to the concept. The concept is the “thing to be measured” in a patient-centered outcome. The concept may be broadly defined such as “emotional function,” or “physical functional performance,” or “symptoms of Crohn’s disease.” The concept may also be more narrowly defined such as “depressed mood,” “time to walk a specified distance without assistance,” or “stool consistency and frequency.” The selection of the concept of interest is most often related to the logic of using the concept and its measurement in establishing efficacy of a treatment [4].

Iteratively with identifying and defining the concept of interest comes the third task of defining the context of use for the planned clinical trial starting with identification of the study entry criteria. This task is based on the results of patient engagement along with relevant scientific literature, and input from the clinical and caregiver communities. The positioning of endpoints in the planned clinical trials will be based on this input to ensure that the study design and analysis plan will permit the most important information to be produced and interpreted, based on patient input. The “context of use” factors in Figure 4 are important to consider in determining the adequacy of a patient-centered outcome to measure treatment benefit. The target population, the clinical trial design and objectives, and the actual setting of the study within clinical practice are key considerations. To establish the PCO in the trial program, early and frequent consultation with the FDA is advised by “starting with the end in mind,” stating the measurement objective and the desired conclusions or claims based on the measured treatment benefit of the medical product.

Instrument development begins by eliciting the content of a COA to measure the intended concept. This process has been well-outlined in two articles on establishing content validity of PRO instruments [5,6]. Although the context is medical product labeling, the principles apply equally for measures to be used in research. Establishing content validity means assuring that all facets of a given concept are represented in the construct or measure of that concept. A measure of psychological functioning, for example, would have poor content validity if no assessment of cognitive functioning were included along with emotional functioning.

![Figure 3. Patient-Centered Outcome Tool Development Optimally Occurs in the Translational Stage of Medical Product Development](image)

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**Figure 1. Patient-Centered Outcomes: A Definition**

Those outcomes important to patients’ survival, function, or feelings as identified or affirmed by patients themselves, or judged to be in patients’ best interests by providers and caregivers when patients cannot report for themselves.

**Figure 2. Key Steps or Requirements in Using Patient-Centered Outcomes in Drug Development and Research**

1. Patient engagement through all phases of drug development and research
2. Identification of the concept of interest and rationale for use
3. Definition of how patient-centered outcome is a treatment benefit within a proposed context of use
4. Keeping the patient-perspective in mind during conduct of clinical research
5. Qualification of COAs for regulatory purposes or use of COA in clinical trial

**Figure 4. Context of Use for a Clinical Trial with Patient-Centered Outcomes**

- **Disease definition and patient subpopulation**
  - Disease subtype
  - Disease severity
  - Time since diagnosis and history of previous treatment
  - Patient demographics
- **Clinical trial design and objectives**
  - Endpoint positioning
  - Endpoint definitions
  - Analysis plan
  - Methods for interpretation of study results
  - Targeted labeling claim(s)
- **Clinical practice and study setting**
  - Inpatient vs. outpatient
  - Geographic location(s)
  - Clinical practice variations

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Finally, the entire process of using PCOs in the regulatory process can be shortened by considering the use of COAs that have been qualified for the context of use planned. Regulatory qualification of COAs offers the potential for the identification of such COAs [7]. The FDA and the EMA are harmonizing their processes and standards for COA qualification review. These agencies suggest concurrent submissions of identical dossiers for parallel review of the outcome assessment. When submitting a New Drug Application or Biologics Licensing Application that includes a new COA, it is recommended that applicants also seek qualification independent of the action on the new product. Although no COAs have yet been qualified under these new regulatory programs, examples of COA qualification projects currently underway are contained in Figure 5.

Table: Examples of Current COA Qualification Projects

<table>
<thead>
<tr>
<th>Disease (Consortium)</th>
<th>Patient Centered Outcome Under Development</th>
<th>COAs Used in the Past to Support Related Labeling Claims</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exacerbations of chronic pulmonary disease (EXACT PRO Consortium)</td>
<td>Acute on COPD symptoms</td>
<td>Medically treated exacerbation events</td>
</tr>
<tr>
<td>Acute bacterial skin and soft tissue infections (NHANES)</td>
<td>COPD/respiratory symptoms</td>
<td>Long function, rescue meds</td>
</tr>
<tr>
<td>Community acquired bacterial pneumonia (CAPP)</td>
<td>MEWS symptoms</td>
<td>Complete response (CAPP)</td>
</tr>
<tr>
<td>Rheumatoid Arthritis (COPM PRO Consortium)</td>
<td>GBS symptoms</td>
<td>Complete resolution (COPM)</td>
</tr>
<tr>
<td>Functional Hypothesis (COPM PRO Consortium)</td>
<td>Fatigue in RA</td>
<td>NA</td>
</tr>
<tr>
<td>Non-Small Cell Lung Cancer (COPM PRO Consortium)</td>
<td>ED symptoms</td>
<td>NA</td>
</tr>
<tr>
<td>Depression (COPM PRO Consortium)</td>
<td>NSCLC symptoms</td>
<td>NA</td>
</tr>
<tr>
<td>Cystic Fibrosis (Cystic Fibrosis Foundation)</td>
<td>Major depressive episode symptoms (PRO)</td>
<td>Clinician rating of depression severity</td>
</tr>
<tr>
<td>Asthma (COPM PRO Consortium)</td>
<td>CF acute pulmonary exacerbations</td>
<td>Medically treated events</td>
</tr>
<tr>
<td>Asthma (COPM PRO Consortium)</td>
<td>Asthma symptoms</td>
<td>Asthma symptoms</td>
</tr>
<tr>
<td>Asthma (COPM PRO Consortium)</td>
<td>AR symptoms/signs</td>
<td>Single-item patient reported rating of change</td>
</tr>
<tr>
<td>Cognition in patients with MCI (COPM PRO Consortium)</td>
<td>Complex ADLs &amp; inter-personal functioning</td>
<td>NA</td>
</tr>
<tr>
<td>FLU PRO (NIAD &amp; CDC)</td>
<td>Flu symptoms (adult and ped)</td>
<td>NA</td>
</tr>
<tr>
<td>Cancer Fatigue (MOOC-1 Consortium)</td>
<td>CA-related fatigue symptoms</td>
<td>Flu symptoms</td>
</tr>
</tbody>
</table>

Although qualification is not required and entirely voluntary on the part of sponsors, many potential benefits exist in the qualification process. The COA can be applied in drug development programs without the need for submission and re-review of extensive supportive information for each IND. This may make the COA more attractive to use as well as encourage development of therapies for the disease.

The use of PCOs in drug development and research requires that we change our culture and focus on the difficult work of conceptualizing treatment benefit early in the development of the intervention. PCOs provide the information that all stakeholders need to make difficult decisions on the efficacy of a medical product. Patient engagement makes the entire research process more credible and relevant to the actual use of the intervention. The more closely related the outcome assessment is to how patients survive, feel and function in their daily life, the more likely we shall find treatment benefit that is meaningful to all stakeholders in health care.

The era of the patient-centered outcome is at hand. It is up to members of ISPOR and others in our health research community to ground their research in the patient perspective and forge treatments that are responsive to the specific needs and concerns of the many different patient groups internationally.

REFERENCES