Using PROs to Measure What Matters Most to Patients in Clinical Trials

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The Value of PROs

In this long overdue era when data from the patient perspective are being used to assess the safety, effectiveness, and value of medical products, the acceptance and use of Patient-Reported Outcomes (PROs) in clinical trials continues to increase and is valued by various parties. The impetus is largely due to an overall shift from a system based solely on patient risk to a benefit-risk strategy informed in part by patient input.

The growing trend towards patient engagement throughout all stages of product development stems not only from the pleas of patient advocacy groups, but from professional societies, regulatory bodies and third-party payers alike. From the year 2000 through 2015, the Center for Devices and Radiologic Health (CDRH) observed over a 500% increase of pre-market submissions including PRO measures (PROMs)[1]. In 2017, in alignment with CDRH strategic priorities, more than 75% of approved, pivotal original and new study IDEs included PROs in support of the submission[2]. FDA's first guidance on PROs, in 2009[3], interprets what is meant by "well-defined and reliable" for PRO measures intended to provide evidence of treatment benefit. Since this time, several guidance documents have been published from various organizations on different aspects of PRO use such as PROM development,[4-6] PRO-specific protocol guidance[7] and collection and reporting.[8-10]

The FDA defines a PRO as *"any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else"* [11]. PROMs are standardized, scientifically developed, and accurately tested instruments (usually questionnaires or scales) that capture practical and distinctive information from the patient's point of view, that biomedical and clinician-driven outcomes inherently cannot obtain (e.g., symptoms of pain, fatigue, anxiety; frequency and severity of symptoms; symptom interference on daily function; treatment satisfaction). The integration of PROs with traditional endpoints in clinical trials provides a comprehensive evaluation of the intervention under study. Data derived from PROs can provide valuable evidence for benefit-risk assessments that can be used to communicate the effect of a treatment on patient symptoms, functioning and quality of life on medical device labels and are subsequently useful for market adoption and consideration as part of value-based framework assessments.[3] Including patients in the development and/or selection of clinical outcome assessments is particularly beneficial as they can identify core symptoms and the relationship of symptoms on daily functioning that are characterized by the disease. This patient guidance serves to inform the outcome concepts that represent the disease and treatment impact, by delineating what aspects are truly clinically relevant from the patient perspective in evaluating treatment benefit.

Selecting the Right Tool

The value PROs add to clinical trial data is well accepted; the challenge is in developing or selecting the right instrument for your trial to produce clinically meaningful data in order to meet regulatory requirements for labeling. The FDA has rejected labeling on the basis that the PROM selected was not appropriate for the clinical trial and/or due to lack of appropriate PRO development and validation[12].

Whether used to support primary or secondary endpoints, experts in the field and FDA agree a disease or condition-specific PRO that measures proximal outcomes, such as symptoms, versus measuring more distal, multi-dimensional, or global constructs such as health-related quality of life (HRQOL), are more effective. Symptoms are directly related to the disease and treatment effect while there is an indirect relation to HRQOL[13]. The need to alleviate symptoms and/or improve functional limitations are often the main objectives of drug or device treatments and are ultimately the reason why patients seek medical care. Another advantage, disease-specific PRO instruments address more clinically relevant domains and are therefore more

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sensitive to improvement derived from the intervention. General HRQOL tools are more likely to be influenced by factors other than the trial intervention, such as general social circumstances and life events[13].

Initial steps in selecting a PRO appropriate for your study include conducting a thorough literature search in the therapeutic area to truly understand your patient population and determine if a properly validated disease-specific instrument already exists. Consulting with clinicians, key opinion leaders, investigators, professional societies, and patient advocacy groups in the therapeutic area can also be informative due to the breadth of experience and varying stakeholder interest as you consider study endpoints. Professional societies may have proposed approaches and recommendations for evaluating new therapies that warrant consideration. Your endpoints or measurement goals should drive your instrument selection such as what areas (domains) would be expected to change with the study intervention (e.g., pain, functional status, anxiety).

Consider the following suggestions in selecting a PROM:

- Determine what the PRO-related research questions are early in the study design
- Identify the particular domains affected by the condition and those expected to change with the intervention within the timeframe of the study
- Select a PRO that is proximal to the disease or treatment (i.e., symptoms/treatment side effects)[14]
- Review the PROM description to assess what domains of function it measures and the appropriate developmental age for administration
- Determine whether the individual PRO questions are relevant to the study population and study question of interest
- Evaluate the psychometric properties of the PRO measure including content and construct validity, reliability (particularly test-retest), and ability (sensitivity) to detect change
- Assess practical factors such as the recall period, respondent burden, mode of administration, and the need for validated language translation[14]

Whether for a primary or secondary endpoint, if a PRO will be used, a PRO-specific research question and rationale for a PRO assessment need to be formulated. A clearly defined question helps with the selection of measures and specification of hypotheses (i.e., the prediction(s) sought to be tested and verified) which should be included in the study protocol. Specifying a clearly defined hypothesis in advance prompts sponsors and investigators to carefully consider the constructs (domains) of particular relevance to the clinically driven and relevant study question and thereby facilitates selection of appropriate PRO measures[10]. PRO measures that are not suited to the specific research question cannot yield the required information and may be viewed as unessential by study staff and participants leading to wasted resources in collecting PRO data.

To assist sponsors and investigators in awareness of the utility of PROs in a particular device or therapeutic area, CDRH issued a report on the Value and Use of PROs in Assessing Effects of Medical Devices[1], which included detailed case studies of PRO use in submitted medical device studies (Appendix I) and an CDRH PRO Compendium (Appendix II). While not an exhaustive list, the compendium provides examples of PRO used in various therapeutic areas.

Other Helpful Resources: NIH-sponsored PROMIS® Suite and NIH Toolbox through HealthMeasures

In 2004, the National Institutes of Health (NIH) partnered with a group of scientists, via grant funding, to form the PRO Measurement Information Systems (PROMIS). The PROMIS suite provides over 300 interchangeable measures or item banks that measure health-related PRO domains. These measures have been standardized to provide metrics across a wide range of conditions and diseases, and many are available in several languages. The PROMIS measures have been rigorously tested and validated, are efficient (to minimize respondent burden) and precise (greater precision enhances power to reduce need for large sample size), and are available in most instances at no charge at healthmeasures.net. Also provided is information to help users select, administer, score, and interpret the measures. To explore recommendations on the domains and measures for a specific population (e.g., heart failure, diabetes), search here.

In 2016, the NIH transitioned the management of the PROMIS measures to Northwestern University where the services provided are maintained on a non-profit basis. These services, along with an online Resource Center with various administration and data collection tools (e.g., iPad apps, computer adaptive tests [CATs], REDCap, EPIC and other online tools), are available for a reasonable cost for commercial use.

In the case of rare diseases or therapeutic areas with sparse research, especially as it pertains to PROs, there simply may not be an appropriate validated instrument for use, necessitating development of a "from scratch" PRO assessment tool. Developing a PRO assessment tool can be challenging as well as timely and costly. Resources are available providing guidance on this process such as the two-part International Society for Pharacoeconomics and Outcomes Research (ISPOR) *PRO Good Research Practices Task Force Report.* This document provides a step-by step process for developing a PRO instrument and executing and reporting studies to support the content validity.

Summary

Including PROs in a clinical trial can be useful for labeling, marketing claims and market adoption, but selecting an appropriate PROM requires careful thought regarding the specific research questions to be addressed and the needs of all stakeholders, including patients, sponsors, clinicians, and regulatory authorities. Device manufacturers must ensure trial design, study endpoints, and selected PRO measures generate meaningful patient data that can be beneficial throughout the device lifecycle.

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