Including Patient-Reported Outcomes and Patient-Reported Resource-Use Questionnaires in Studies

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Rationale: More efficient and better informed healthcare systems are expected to have improved knowledge of the impact of interventions on patient outcomes and resources used by patients and providers in specific health conditions.

Objectives: To describe trends related to putting patients at the center of healthcare decision making, regulatory trends and best practice recommendations for developing high-quality patient-reported outcomes (PROs), and strategic issues related to including PROs in studies.

Materials and Methods: We summarize PRO concepts, definitions, and broadly-accepted scientific standards for developing, assessing, and interpreting PROs. Three conceptual models are presented as examples for assessing PROs in relation to other outcomes. We discuss different perspectives for stakeholders, including regulatory issues pertaining to formal guidance for PRO development and for use in trials. We provide examples of PROs used in studies for assessing health outcomes in oncology and resource-use outcomes in low back pain patients.

Results: Psychometric scientists working closely with multi-disciplinary teams and regulatory authorities have greatly improved the science of collecting, assessing, and understanding patient-reported outcomes in clinical trials. A simplified framework is presented for strategic considerations for including PROs in studies, such as the appropriate timing for PRO endpoints. Asking patients about their health status and/or use of resources improves our understanding of how interventions and care processes may impact their lives and their budgets. We provide examples from a back pain trial of patient-reported resource-use questionnaires for medicines taken and other services or products used by patients.

Conclusions: Healthcare stakeholders are placing increased emphasis on resource use and the impact of interventions on patients, including effects associated with diagnostic tests. Patient-reported outcomes are being used in clinical practice and in clinical research, supported by formal best-practice guidelines. Radiology has a role as an engaged stakeholder in the design, conduct, and interpretation of patient-based evidence, and in its relevance to health policy implementation.

Key Words: Patient-reported outcomes; clinical studies; radiology; endpoints; health outcomes.

Patient-reported outcomes (PROs) provide valuable health information. Patients, providers, and health systems are being encouraged and incentivized to involve patients and their families more directly in health care decision making. Examples of support for additional evidence development related to patient outcomes in the United States include the creation of the Patient-Centered Outcomes Research Institute (PCORI) (1), published priorities in comparative effectiveness research (CER) (2–4), and the Agency for Healthcare Research and Quality's (AHRQ's) emphasis on patient-centered outcome research (5). "Patient-centered outcomes research (PCOR) helps people and their caregivers communicate and make informed health care decisions, allowing their voices to be heard in assessing the value of health care options" (1). Patient input is being sought in developing research priorities, informing shared decision-making models, selecting meaningful outcomes for clinical research, and disseminating information to patients and providers. Consequently, PROs and other relevant patient-reported data have become more ingrained in clinical research, observational research, clinical care, and quality improvement initiatives.

In addition to engaging patients in research and in their health care decision making, PROs are also valuable to more comprehensively measure treatment benefits and harms in clinical research and CER. Manufacturers may choose to include PROs in clinical trials to assess the impact of interventions on patients, which has potential use in marketing their products. Clinicians, health outcomes researchers, payers, or health policy makers may desire PRO data to identify optimal strategies to improve outcomes, whether related to increasing positive health effects in patients or reducing harms and/or negative effects.

In this article, we provide a general overview of PROs and published recommendations for their inclusion in clinical

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trials. We review definitions specific to PROs and identify US-based and international guidance related to regulatory processes and standards. Specifically, we outline recommendations associated with evidence generation using PROs in studies to support labeling claims (6–8). We use simplified graphics to depict strategic issues, provide examples of patient-reported diaries and PRO questions, and list practical aspects of including PROs and resource-use questionnaires in research.

SCIENTIFIC STANDARDS FOR PROS

General Guidance on Including Patient-Based Outcomes in Studies

The development of and appropriate use of high-quality PROs require scientific expertise, time, and substantial expense associated with questionnaire (instrument) development, testing, validation, and refinement. Multiple disciplines have collaborated in developing strong guidance on health outcomes measurement, developing PROs and resource-use instruments, and incorporating PROs in clinical research. Extensive texts by experts in PRO development, analysis, and interpretation provide guidance on designing instruments, selecting instruments, and assessing responses (9,10). These multidisciplinary works have focused on

- Defining health and health domains,
- Measuring physical, social, and psychological well-being,
- Unique issues in assessing mental status, pain, and general health status and quality of life (QOL),
- Including QOL or other PRO scales in clinical trials,
- Scales, tests, and measures,
- Selecting and administering instruments,
- Analyzing, interpreting, and presenting PRO data,
- Distinct perspectives, including cultural and language issues, and
- Issues and implications in health policy and health economics.

A US Food and Drug Administration (FDA) Web site descriptively and graphically outlines their Clinical Outcomes Assessment (COA) Qualification Program, including discussion of four types of outcomes: PROs, clinician-reported outcomes, observer-reported outcomes, and performance outcome measures (11). The educational information outlines the US FDA's COA-focused "wheel" representing the components of PRO instrument development processes. It contains five spokes outlining steps to follow in evaluating a "concept of interest for a claim:"

- Identify content of use and concept of interest,
- Draft instrument and evaluate content validity,
- Cross-sectional evaluation of other measurement properties,
- Longitudinal evaluation of measurement properties/interpretation methods, and
- Modify instrument.

Other resources are available to provide scientific guidance on PRO measurement (12), recommendations for documenting PRO-based data via PRO Evidence Dossiers, eliciting concepts for PROs, and assessing respondent understanding (13–15).

Definitions and Desired Properties of PROs

More psychometric research has been conducted in the assessment of patient-reported health outcomes, such as in symptom severity or symptom impact scales and health-related quality-of-life (HRQOL) measures, compared to research on the best approaches to collecting resource-use data or financial end points, such as patient expenditures or their willingness to pay for specific interventions. Important data may not be captured in electronic records or may be difficult to assess via patient observation or physical examination. In the absence of more objective tests or mechanisms (eg, blood pressure monitor), we can ask patients how they feel, their levels of symptoms, and how their symptoms impact their lives, as well as their general ability to function in their personal lives or in social settings. For patient-reported data, scientific principles have centered on using appropriate language, clarity, and structure for asking questions, the scoring of and evaluation of responses in instruments, analyzing PRO data in comparative studies, determining clinical meaning and meaning to the patient for changes in outcomes, and assessing how representative or generalizable findings may be for health systems.

Desired properties of patient-reported instruments are rooted in methods of survey-based research and cognitive psychology. The following are standard definitions for standard characteristics of well-tested health outcomes measures (8):

- *Measurement (psychometric) properties:* All the attributes relevant to the application of a PRO instrument including the content validity, construct validity, reliability, and ability to detect change (responsiveness).
- *Content validity:* Evidence from qualitative research demonstrating that the instrument measures the concept of interest including evidence that the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use. Testing other measurement properties will not replace or rectify problems with content validity.
- *Construct validity:* Evidence that relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups.
- *Reliability:* The ability of a PRO instrument to yield consistent reproducible estimates of true treatment effect.
- *Ability to detect change (responsiveness):* Evidence that a PRO instrument can identify differences in scores over time in individuals or groups who have changed with respect to the measurement concept.

Conceptual Models Providing Context for PROs

We provide three examples of models for conceptualizing how patient outcomes and PROs may be framed in relation to other measures/outcomes.