New Frontiers in Patient-Reported Outcomes: Adverse Event Reporting, Comparative Effectiveness, and Quality Assessment

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Abstract
Patient-reported outcomes (PROs) are data elements directly reported by patients or their surrogates about experiences with care, including symptoms, functional status, or quality of life. PROs have commonly been evaluated in clinical trials for drug and medical device development. Interest is growing in the ability to integrate PROs into additional contexts, particularly product safety evaluation, comparative effectiveness research, and measurement of care quality. This interest reflects a growing focus on patient-centeredness in health care broadly and on provisions of the US Patient Protection and Affordable Care Act of 2010. Multiple initiatives demonstrate the feasibility and value of patient reporting in these areas. Inclusion of PROs in electronic health records and hospital patient portals, as well as longitudinal registries, can facilitate use of these data for multiple analytic purposes as well as enhance delivery of care and patient-provider communication. Challenges include the logistics and cost of implementing PRO programs; missing data, particularly from hard-to-reach and ill patients; and the need for standardization of outcome measures and electronic data representation. These challenges have been surmounted in limited initiatives and now must be translated to larger implementations.
INTRODUCTION

Over the past several decades, the science of developing, administering, and analyzing patient questionnaires has advanced substantially (1). Patient-reported outcome (PRO), a term that has emerged recently, encompasses myriad areas of the patient experience that can be measured, such as symptoms, quality of life, functional status, satisfaction with care, or medication compliance—essentially anything that patients know and is appropriate for them to report. Indeed, the US Food and Drug Administration (FDA) defines a PRO as “any report of the status of a patient’s health condition that comes directly from the patient [or in some cases a caregiver or surrogate], without interpretation of the patient’s response by a clinician or anyone else” (2, p. 2).

Until recently, most scientific activity around PRO questionnaires (also referred to as instruments, measures, or tools) focused on clinical trials, particularly drug development (1, 3). Key components of the PRO measure development process have included qualitative methods for eliciting direct patient input (4, 5) as well as quantitative methods for assessing measurement properties such as construct validity, reliability, sensitivity, appropriate recall period, and thresholds representing meaningful score changes (2). These tools have often been used in clinical trials to support other endpoints, such as survival, although PROs have also been primary endpoints, most notably when assessing products focused on symptom alleviation (e.g., analgesics, antiemetics) (6, 7). PROs have played a role in many regulatory drug approvals and labels in the United States and abroad (7–9).

Recently, interest has emerged in the use of PRO measures in a host of additional health care contexts. In the United States, this interest has been reflected in, and prompted by, the US Patient Protection and Affordable Care Act (ACA) of 2010. The ACA includes several specific provisions to increase the patient-centeredness of research and care delivery (10). Since the passage of the ACA, in the United States there has been a marked increase in publications, funding announcements, and initiatives focused on patient-centeredness (11). A new term coined in the legislation, patient-centered outcomes research (PCOR) is distinct from PROs and largely refers to methodologies of comparative effectiveness research but has a greater focus on study designs and results that are meaningfully connected to decisions faced by real patients (12). As such, there is a close connection to PROs, in that the best way to elicit the perspective of patients in PCOR is via PRO measures. Most prospective PCOR studies include collection of PRO data (13). Of particular note in the ACA is creation of the Patient-Centered Outcomes Research Institute (PCORI), a new funding agency that supports PCOR (10).

Three novel uses of PROs are (a) assessment of adverse events (i.e., the harms or safety of care), (b) comparative effectiveness research, and (c) quality assessment (also called performance evaluation). These areas have emerged within the broader context of patient-centeredness and reflect a growing focus on the patient experience in clinical research and care delivery. The increased feasibility and affordability of collecting data from patients via wireless technologies has also prompted interest in PROs. PRO measures are already integrated into several commercially available patient portals, electronic health record systems, and clinical trial management systems (14).

PATIENT-REPORTED OUTCOMES FOR ADVERSE EVENT REPORTING

Traditionally, clinicians have documented the harms of care. In clinical trials, clinical investigators document adverse events in medical charts, and then data managers transcribe this information into central databases. Similarly, during clinical care, providers elicit and record information about adverse events in charts. Many of these events are symptoms such as fatigue, pain, peripheral sensory neuropathy, or nausea.
A substantial body of literature demonstrates that clinicians miss or underestimate a large proportion of the symptomatic adverse events experienced by patients (Figure 1) (15–17). Moreover, clinician assessment of adverse events is relatively unreliable, meaning that if two different clinicians evaluate the same patient, they often disagree with each other’s assessment (Table 1) (18). Patient reporting is substantially more reliable, and numerous studies have shown it to be feasible (19). Most patients are willing and able to self-report their experiences with treatment: feasibility studies demonstrate that when PROs are collected well (i.e., using contemporary electronic data capture methods and reminder calls to patients), compliance can exceed 95% in clinical trials and 80% in real-world routine care settings (20).

In clinical research, standards for assessing symptoms related to efficacy (e.g., joint pain improvement with a new arthritis drug) versus symptoms related to safety (e.g., joint pain caused by a new aromatase inhibitor) are inconsistent (15, 21). For the former, PROs have become the gold standard, as stated in guidance documents from the US FDA and European Medicines Agency (2). But for the latter, clinician reporting has remained standard.

Researchers, product developers, and regulatory agencies are increasingly interested in including patient assessments of adverse events in clinical trials (21). In several cases, patient-reported data about the comparative tolerability of products have played a key role in drug approval and labeling, for example, in the cases of imitinab (better tolerated than interferon) and pazopanib (better tolerated than sunitinib). Numerous pharmacovigilance programs are already integrating structured patient reporting, with evidence of improved detection of treatment risks (21, 22).

The principal barrier to more widespread use of this approach is a concern among some drug developers that patient reporting will increase rates of reported adverse events, altering the risk-benefit balance unfavorably. But evidence suggests that patient reporting better detects baseline (pretreatment) symptoms, thereby actually reducing the cumulative incidence of adverse events detected during treatment in comparison with clinician reporting (15). Cost and logistical challenges are also sometimes cited, but many trials have demonstrated a low relative cost compared to other data sources, with PRO correlative endpoints representing less than 3% of a given study budget (20). Use of PROs in clinical research in general is on the rise; approximately 25% of US drug labels now include PRO-derived data (8).

PATIENT-REPORTED OUTCOMES IN COMPARATIVE EFFECTIVENESS RESEARCH

Until recently, PROs were not commonly included in prospective comparative effectiveness research (CER) designs such as registries or cohort studies (11, 23). Interest in this area has increased in part due to funding from PCORI and from the US Agency for Healthcare Research and Quality (AHRQ), which receives support in part from a PCOR trust fund established by the ACA.

As a part of its legislative mandate, PCORI developed a Methodology Report containing standards for the design of CER and PCOR (12). Although the purpose of this report is to direct investigators seeking PCORI funding regarding preferred approaches, it has been widely disseminated and cited as a gold standard for methodology. The report contains a chapter on patient-centeredness in which several standards are listed (Table 2). These patient-centeredness standards emphasize the importance of involving patients in every step of the research process. When planning a study, patient informants should be consulted either as advisors or through qualitative methods. Selected outcomes must be demonstrated to be meaningful and important to the target population. PROs should be included whenever selected outcomes are known best to patients, and a dissemination plan for results should consider how to reach relevant patient populations.

PCORI’s standards around the use of PROs were informed by commissioned systematic literature reviews and landscape overviews...
Figure 1
Cumulative incidence of clinician-reported (blue) versus patient-reported (gold) symptomatic adverse events over time at successive office visits in cancer clinical trials (N = 850). Clinicians underdetect these symptoms in comparison with patients. The downstream effect is underreporting of symptoms in clinical trial publications and drug labels. Reproduced with permission from Reference 15.
Table 1  Clinician inter-rater agreement on the grading of adverse events

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<th>Symptom</th>
<th>Intraclass correlation coefficient</th>
<th>95% Confidence interval</th>
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<td>Constipation</td>
<td>0.48</td>
<td>0.36; 0.58</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.58</td>
<td>0.49; 0.66</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>0.69</td>
<td>0.62; 0.75</td>
</tr>
<tr>
<td>Fatigue</td>
<td>0.50</td>
<td>0.39; 0.59</td>
</tr>
<tr>
<td>Nausea</td>
<td>0.52</td>
<td>0.41; 0.60</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>0.71</td>
<td>0.65; 0.76</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.46</td>
<td>0.34; 0.56</td>
</tr>
</tbody>
</table>

*Grading was compared between clinicians who saw the same patient on the same day and independently graded adverse events using intraclass correlation coefficients (ICCs) (N = 400). Most agreement is moderate, with ICCs lower than generally desirable for research-grade data sources. Reproduced with permission from Reference 18.

(24, 25). Other organizations, such as the International Society for Quality of Life Research (1), have published similar standards. A recent AHRQ methodology manual also includes details on the use of PROs in registries (26).

There are many examples of broad implementation programs. In England, all patients undergoing selected elective surgical procedures receive baseline and follow-up questionnaires about symptoms and functional status (27). In Sweden, numerous national registries across disease types include systematic PRO assessment. The province of Ontario, Canada, has installed computer kiosks for collecting PRO data in most oncology clinics (28). In each of these instances, data are used to assess the comparative effectiveness of treatment strategies. The pharmaceutical industry commonly includes PROs in postmarketing observational studies and increasingly wishes to include them in late-phase comparative studies (20).

PATIENT-REPORTED OUTCOMES FOR QUALITY ASSESSMENT

Several recent US initiatives have emphasized the need to use PROs in the assessment of quality of care (also referred to as performance evaluation) (29–31). Historically, assessing patient experiences with care delivery (e.g., satisfaction with care) has been common, for example, using AHRQ’s Consumer Assessment of Healthcare Providers and Systems (CAHPS) survey (32). Assessment of symptoms, quality of life, or functional status, however, has been much less common. A new term, patient-reported outcome performance measure (PRO-PM), was recently coined by the National Quality Forum (NQF) to refer to such assessments and is defined as “a performance measure that is based on PRO data aggregated for an accountable health care entity” (31, p. 139, box 1).

An example of a PRO is depressed mood; a related PRO measure is the Patient Health Questionnaire (PHQ-9) depression module. An example of a PRO-PM from the PHQ-9 is the proportion of patients with a diagnosis of major depression or dysthymia and initial PHQ-9 score > 9 who demonstrate remission at 6 months with a follow-up PHQ-9 score < 5 (NQF endorsed measure #0711) (33).

Multiple initiatives are already implementing PRO-PMs. For example, the state of Minnesota requires primary care and psychiatry practices to serially administer the PHQ-9 to patients with depression to track progress (33). The US Medicare Advantage Program systematically administers the Health Outcomes Survey to selected plan participants (34). Patients across Sweden with rheumatologic illnesses complete questionnaires that are linked to the national electronic health record system (35). Patients participating in a Boeing-sponsored patient-centered medical home pilot program longitudinally complete questions about physical and mental health (36).
<table>
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<th>Standard</th>
<th>Description</th>
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<td>Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context</td>
<td>People representing the population of interest include individuals who have the condition or who are at risk of the condition and, as relevant, their surrogates or caregivers. Other relevant stakeholders may include clinicians, administrators, policy makers, or others involved in health care decision making. Stakeholders can be engaged in the processes of: Formulating research questions; Defining essential characteristics of study participants, comparators, and outcomes; Identifying and selecting outcomes that the population of interest notices and cares about (e.g., survival, function, symptoms, health-related quality of life) and that inform decision making relevant to the research topic; Monitoring study conduct and progress; and Designing/suggesting plans for dissemination and implementation activities. When applicable, research proposals should describe how these stakeholders will be identified, recruited, and retained. If engagement is not necessary or appropriate in these processes, explain why.</td>
</tr>
<tr>
<td>Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest and ensure that data are collected thoroughly and systematically from all study participants</td>
<td>Research proposals and subsequent study reports should describe: (a) the plan to ensure the representativeness of participants; (b) how participants are identified, selected, recruited, enrolled, and retained in the study to reduce or address the potential impact of selection bias; (c) efforts employed to maximize adherence to agreed-on enrollment practices; and (d) methods used to ensure unbiased and systematic data collection from all participants. If the population of interest includes people who are more difficult to identify, recruit, and/or retain than other study populations (for example, individuals historically underrepresented in health care research such as those with multiple disease conditions, low literacy, low socioeconomic status, or poor health care access, as well as racial and ethnic minority groups and people living in rural areas), then specify plans to address population-unique issues for participant identification, recruitment, and retention.</td>
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<tr>
<td>Use patient-reported outcomes when patients or people at risk of a condition are the best source of information</td>
<td>When patients or people at risk of a condition are the best source of information regarding outcomes of interest, the study should employ patient-reported outcome (PRO) measures in lieu of, or in addition to, measures derived from other sources. Proposals should describe: (a) the concept(s) underlying each PRO measure (e.g., symptom or impairment) and how the measure is meaningful to, and noticed by, patients in the population of interest; (b) how the concept relates to the health decisions the study is designed to inform; (c) how the PRO measure was developed, including how patients were involved in the development; and (d) evidence of measurement properties including content validity, construct validity, reliability, responsiveness to change over time, and score interpretability, including meaningfulness of score changes in the population of interest with consideration of important subgroups. If these measurement properties are not known, a plan for establishing the properties must be provided. Caregiver reports may be appropriate if the patient cannot self-report the outcomes of interest. If PROs are not planned for use in the study, justification must be provided.</td>
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<td>Support dissemination and implementation of study results</td>
<td>Support dissemination and implementation of study results by suggesting strategies, indicating clinical and policy implications, and working with patients or organizations to report results in a manner understandable to each target audience.</td>
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*Published by the Patient-Centered Outcomes Research Institute in December 2012; [http://pcori.org/assets/PCORI-methodology-standards.pdf](http://pcori.org/assets/PCORI-methodology-standards.pdf). Investigators applying for PCORI funding generally must adhere to these standards for research projects.*
Several professional organizations are developing condition-specific PRO-PMs. For example, the American Society of Clinical Oncology is creating PRO-PMs for symptoms and functional status relevant to the treatment of cancers for implementation in its Quality Oncology Practice Initiative network. The Society of Thoracic Surgeons and American College of Cardiology recently developed a registry including assessment of patient-reported health-related quality of life as part of a Centers for Medicare & Medicaid Services (CMS) National Coverage Determination program for percutaneous transcatheter aortic valve replacement (37).

To assist performance measure developers in creating and administering PRO-PMs, the NQF developed a pathway for creating these measures, which was published in early 2013 (Figure 2) (31). This process begins with establishing a rationale for evaluating PROs in a particular performance evaluation context and identifying outcomes that are meaningful to patients in that context. Procedures for selecting or developing appropriate PRO measures and specifying PRO-PM criteria are described. There is a particular emphasis on including patient input at various points of program development and evaluation.

The NQF pathway is now in active use in multiple initiatives, most notably in collaborative work among the National Committee for Quality Assurance (NCQA), CMS, and the US Office of the National Coordinator for Health Information Technology to identify PRO measurement strategies supported by electronic health records. This work seeks consensus on PROs that are appropriate for specific clinical contexts and on definitions of meaningful improvements in symptoms and functional status.

**DISCUSSION**

As the feasibility and affordability of collecting data directly from patients has improved, interest in harnessing these data in a host of health care contexts has grown. Online communities such as PatientsLikeMe and HealthTalkOnline demonstrate that large numbers of patients are willing and able to share data with each other and with the public. Historically, methodologically rigorous collection of PROs has been limited to clinical trials. More recently, use of PROs has proliferated in routine care settings, electronic health records, observational studies, and quality improvement programs.

A number of challenges remain as PRO collection becomes more widespread; these are shown in Table 3. The experts who have been involved with data collection in these emerging areas typically have not had expertise in PRO methodology (for example, collecting qualitative data or conducting validation studies). Therefore, cross-disciplinary collaboration including PRO experts is advisable when developing programs that feature PROs.

Several innovations in the logistics and science of PRO data collection are applicable regardless of the context, including the use of electronic interfaces (web, handheld device, or automated telephone system); establishing meaningful score changes up front; and ensuring that patients from diverse educational and cultural backgrounds understand the language in questionnaires.

Although the various areas for potential collection of PRO data seem disparate, increasing confluence is occurring as single data sources are harnessed for multiple analytic purposes. For example, when PRO data are collected through electronic health record systems, this information can be used to manage individual patients and track their progress, and it can also be aggregated for safety surveillance systems, effectiveness research, and quality assessment. Therefore, from a policy perspective, harmonization between these various purposes, particularly standardization of questionnaires and electronic data representation for interoperability, is essential.

More broadly, the emerging interest in PROs across healthcare contexts reflects a growing awareness that the patient perspective can be highly informative for understanding the effectiveness, safety, and value of treatments.
1. Identify the quality performance issue or problem
   • Include input from all stakeholders including consumers and patients

2. Identify outcomes that are meaningful to the target population and are amenable to change
   • Ask persons who are receiving the care and services
   • Identify evidence that the outcome responds to intervention

3. Determine whether patient-/person-reported information (PRO) is the best way to assess the outcome of interest
   • If a PRO is appropriate, proceed to step 4

4. Identify existing PROMs for measuring the outcome (PRO) in the target population of interest
   • Many PROMs (instrument/scale/single-item) were developed and tested primarily for research

5. Select a PROM suitable for use in performance measurement
   • Identify reliability, validity, responsiveness, feasibility in the target population

6. Use the PROM in the real world with the intended target population and setting to:
   • Assess status or response to intervention, provide feedback for self-management, plan and manage care or services, share decision-making
   • Test feasibility of use and collect PROM data to develop and test an outcome performance measure

7. Specify the outcome performance measure (PRO-PM)
   • Aggregate PROM data such as average change; percentage improved or meeting a benchmark

8. Test the PRO-PM for reliability, validity, and threats to validity
   • Analysis of threats to validity, e.g., measure exclusions; missing data or poor response rate; case mix differences and risk adjustment; discrimination of performance; equivalence of results if multiple PROMs specified

9. Submit the PRO-PM to NQF for consideration of NQF endorsement
   • Detailed specifications and required information and data to demonstrate meeting NQF endorsement criteria

10. Evaluate the PRO-PM against the NQF endorsement criteria
    • Importance to measure and report (including evidence of value to patient/person and amenable to change)
    • Scientific acceptability of measure properties (reliability and validity of PROM and PRO-PM; threats to validity)
    • Feasibility
    • Usability and use
    • Comparison to related and competing measures to harmonize across existing measures or select the best measure

11. Use the endorsed PRO-PM for accountability and improvement
    • Refine measure as needed

12. Evaluate whether the PRO-PM continues to meet NQF criteria to maintain endorsement
    • Submit updated information to demonstrate meeting all criteria including updated evidence, performance, and testing; feedback on use, improvement, and unintended adverse consequences

Figure 2
Pathway for developing patient-reported outcome-based performance measures (PRO-PMs) published by the National Quality Forum (NQF). Figure reproduced with permission from Reference 31. Abbreviations: PRO, patient-reported outcome; PROM, patient-reported outcome measure. More information about the NQF endorsement criteria is available at http://www.qualityforum.org/docs/measure_evaluation_criteria.aspx.
### Table 3  Challenges and strategies when integrating patient-reported outcomes (PROs) into data collection programs for assessing safety, comparative effectiveness, or quality of care

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<th>Step</th>
<th>Key challenges</th>
<th>Strategies</th>
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<td>Design of a program</td>
<td>Methodological rigor</td>
<td>Include PRO methodological experts early to assist with qualitative assessments of validation studies if warranted.</td>
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<tr>
<td>Questionnaire administration</td>
<td>Patient burden and missing data</td>
<td>Ensure that questionnaires are not excessive in length (ideally fewer than 50 questions, less than 10 min to complete); use electronic data capture when possible with real-time compliance monitoring and telephone call backup for patients who do not comply.</td>
</tr>
<tr>
<td>Broad program implementation</td>
<td>Standardization and generalizability</td>
<td>Use established, well-developed questionnaires whenever possible.</td>
</tr>
<tr>
<td>Dissemination of results</td>
<td>Data representation and cultural resistance</td>
<td>Collaborate with PRO methodology experts to ensure user-friendly reporting of results; publish results of PRO analyses.</td>
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### DISCLOSURE STATEMENT

The author is not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review. The author is a member of the Methodology Committee of the Patient-Centered Outcomes Research Institute, a member of the Board of Scientific Advisors of the National Cancer Institute, and a member of the Board of Directors of the International Society of Quality of Life Research. This article does not represent the views or opinions of those organizations.

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