Patient-Reported Outcomes (PROs)

Ethan Basch, MD, MSc
Definition of a PRO

“A measurement based on a report that comes directly from the patient (i.e., study subject) about the status of a patient’s health condition without amendment or interpretation of the patient’s response by a clinician or anyone else.”

Guidance for Industry
Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

December 2009
Clinical/Medical
What PROs Do We Commonly Measure?

- Symptoms
- Functional status
- “Health-related quality of life” (HRQL)
- Other stuff
  - Satisfaction, medication compliance, care preferences, health behaviors
- Emerging area: “Patient-generated data”
How Do We Collect PRO data? ("Modes")

- P+P
- CATI
- Tablet
- KIOSK
- TEXT
- mApp
- Web
- IVRS
How do I know a Measure is Appropriate in a Given Context?

• Work with an expert
• Identify outcomes of interest
  – Literature review, qualitative research
• Identify a measure(s) that captures those outcomes
• Should have robust psychometric properties
  – Validity, reliability, responsiveness, etc.
Example from Clinical Research

- Phase 3 trial of first-line abiraterone acetate vs. placebo in metastatic castrate-resistant prostate CA
- Identified time to pain progression as key outcome
- Measure: 0-10 NRS from BPI
- Design: Pain assessed every cycle
  - Endpoint: time to ≥2 point increase from baseline
- Also included broad HRQL questionnaire
  - Other symptoms and overall health status
Result: Time to Pain Progression

- **A**
  - **Patients without pain progression (%)**
  - **Median time to progression of mean pain intensity**
    - Abiraterone plus prednisone: 26.7 months (95% CI 19.3–NE)
    - Placebo plus prednisone: 18.4 months (95% CI 14.9–NE)

- **Number at risk**
  - Abiraterone plus prednisone: 546, 428, 358, 289, 221, 167, 141, 90, 41, 9, 0
  - Placebo plus prednisone: 542, 380, 262, 192, 135, 99, 75, 46, 14, 0, 0

- **HR 0.82 (95% CI 0.67–1.00); p=0.0490**
Result: Time to “HRQL” Deterioration

- Abiraterone plus prednisone: Median time = 11.1 months (95% CI 8.6–13.8)
- Placebo plus prednisone: Median time = 5.8 months (95% CI 5.5–8.3)

HR 0.70 (95% CI 0.60–0.83); p<0.0001

Number at risk:
- Abiraterone plus prednisone: 546
- Placebo plus prednisone: 542
Pain Result Included in the FDA Label
PROs in the Alliance

• Health Outcomes Committee
• Embed PRO correlatives in clinical trials
• Conduct primary PRO research
• 21 open studies currently
  – Across multiple diseases and treatment modalities
• Next F2F at Alliance meeting in Chicago
  – May 9, 10:30-12:30 CST
Example Measures

- Multi-symptom measure: MDASI
- HRQL multi-item measure: EORTC QLQ-C30
- Single-item QOL: LASA or PROMIS
- Cost-effectiveness: EuroQoL EQ-5D
- Depression: PHQ-9
M. D. Anderson Symptom Inventory (MDASI) Core Items

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

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<tbody>
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<td>1. Your pain at its WORST?</td>
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<td>2. Your fatigue (tiredness) at its WORST?</td>
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<td>3. Your nausea at its WORST?</td>
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<td>4. Your disturbed sleep at its WORST?</td>
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<td>5. Your feelings of being distressed (upset) at its WORST?</td>
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<td>6. Your shortness of breath at its WORST?</td>
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# EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:  
Your birthdate (Day, Month, Year):  
Today's date (Day, Month, Year): 31

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<thead>
<tr>
<th></th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
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"Physical Functioning" Domain

1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?  
   1 2 3 4

2. Do you have any trouble taking a long walk?  
   1 2 3 4

3. Do you have any trouble taking a short walk outside of the house?  
   1 2 3 4

4. Do you need to stay in bed or a chair during the day?  
   1 2 3 4

5. Do you need help with eating, dressing, washing yourself or using the toilet?  
   1 2 3 4
<table>
<thead>
<tr>
<th>Question</th>
<th>Not at All</th>
<th>A Little</th>
<th>Quite a Bit</th>
<th>Very Much</th>
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<td>6. Were you limited in doing either your work or other daily activities?</td>
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<td>7. Were you limited in pursuing your hobbies or other leisure time activities?</td>
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<td>8. Were you short of breath?</td>
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<td>9. Have you had pain?</td>
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<td>10. Did you need to rest?</td>
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<td>11. Have you had trouble sleeping?</td>
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<td>12. Have you felt weak?</td>
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<td>13. Have you lacked appetite?</td>
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<td>14. Have you felt nauseated?</td>
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<td>15. Have you vomited?</td>
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<td>16. Have you been constipated?</td>
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### During the past week:

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<th>Question</th>
<th>Not at All</th>
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<td>17. Have you had diarrhea?</td>
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<td>18. Were you tired?</td>
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<tr>
<td>19. Did pain interfere with your daily activities?</td>
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<td>20. Have you had difficulty in concentrating on things,</td>
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<td>like reading a newspaper or watching television?</td>
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<td>21. Did you feel tense?</td>
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<td>22. Did you worry?</td>
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<td>23. Did you feel irritable?</td>
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<td>24. Did you feel depressed?</td>
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<td>25. Have you had difficulty remembering things?</td>
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<td>26. Has your physical condition or medical treatment interfered with</td>
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<td>your family life?</td>
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<tr>
<td>27. Has your physical condition or medical treatment interfered with</td>
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<td>your social activities?</td>
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<td>28. Has your physical condition or medical treatment caused you financial</td>
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<td>difficulties?</td>
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</table>
29. How would you rate your overall health during the past week?
   1  2  3  4  5  6  7
   Very poor                           Excellent

30. How would you rate your overall quality of life during the past week?
   1  2  3  4  5  6  7
   Very poor                           Excellent
Why the Sudden Interest in PROs?

• Affordable care act
• Surge of interest in “value”
  – Patient experience is a key component of value
  – Symptomatic patients use services
• Patient advocacy movement
• Social networking and data sharing
• Technology and electronic health records
Multiple Agencies Interested in PROs

- FDA
- CMS
- ONC
- PCORI, AHRQ
- NQF, NCQA
- ASCO
• Use of PROs migrating from historical use in clinical research to other areas of health care
  – Comparative effectiveness research (CER)
  – Performance evaluation (quality assessment)
  – Clinical care
Comparative Effectiveness Research

• ACA redefined the field of CER as PCOR
  – Term now embraced across federal agencies
• PCOR = CER integrating patient perspectives
• Prospective CER/PCOR expected to be meaningful to patients, and to systematically capture their experience (e.g., PROs)
  – Registries, cohort studies, RCTs, etc.
1. Engage people representing the population of interest and other relevant stakeholders in ways that are appropriate and necessary in a given research context
   – *E.g., when selecting research questions, outcomes, comparators*

2. Identify, select, recruit, and retain study participants representative of the spectrum of the population of interest; ensure that data are collected thoroughly and systematically from all study participants

3. Use patient-reported outcomes when patients or people at risk of a condition are the best source of information
Recommendations for Incorporating Patient-Reported Outcomes Into Clinical Comparative Effectiveness Research in Adult Oncology


Examining the patient’s subjective experience in prospective clinical comparative effectiveness research (CER) of oncology treatments or process interventions is essential for informing decision making. Patient-reported outcome (PRO) measures are the standard tools for directly eliciting the patient experience. There are currently no widely accepted standards for developing or implementing PRO measures in CER. Recommendations for the design and implementation of PRO measures in CER were developed via a standardized process including multistakeholder interviews, a technical working group, and public comments. Key recommendations are to include assessment of patient-reported symptoms as well as health-related quality of life in all prospective clinical CER studies in adult oncology; to identify symptoms relevant to a particular study population and context based on literature review and/or qualitative and quantitative methods; to assure that PRO measures used are valid, reliable, and sensitive in a comparable population (measures particularly recommended include EORTC QLQ-C30, FACT, MDASI, PRO-CTCAE, and PROMIS); to collect PRO data electronically whenever possible; to employ methods that minimize missing patient reports and include a plan for analyzing and reporting missing PRO data; to report the proportion of responders and cumulative distribution of responses in addition to mean changes in scores; and to publish results of PRO analyses simultaneously with other clinical outcomes. Twelve core symptoms are recommended for consideration in studies in advanced or metastatic cancers. Adherence to methodologic standards for the selection, implementation, and analysis/reporting of PRO measures will lead to an understanding of the patient experience that informs better decisions by patients, providers, regulators, and payers.
PROs in Quality Assessment

Example: UK PROM Programme

• Questionnaires at baseline and serially following elective surgeries
  – TKR, THR, inguinal hernia, varicose vein
  – Condition-specific and broad HRQL (EQ-5D)

• >250,000 complete

• Analysis at Hospital Trust level
Proportion of Patients with Improved Scores from Baseline

<table>
<thead>
<tr>
<th>Procedure</th>
<th>EQ-5D Index</th>
<th>EQ-VAS</th>
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<td>Groin Hernia</td>
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<td>EQ-5D Index</td>
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<td>Hip Replacement</td>
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<td>EQ-5D Index</td>
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<td>Knee Replacement</td>
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<td>EQ-5D Index</td>
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<td>Oxford Knee Score</td>
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<td>Varicose Vein</td>
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<td>EQ-5D Index</td>
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<tr>
<td>Aberdeen Varicose Vein Score</td>
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Got Worse | Improved

- Groin Hernia: EQ-5D Index (49.3%), EQ-VAS (38.2%)
- Hip Replacement: EQ-5D Index (87.2%), EQ-VAS (61.4%), Oxford Hip Score (95.7%)
- Knee Replacement: EQ-5D Index (77.6%), EQ-VAS (50.2%), Oxford Knee Score (91.4%)
- Varicose Vein: EQ-5D Index (52.4%), EQ-VAS (40.4%), Aberdeen Varicose Vein Score (83.4%)
Performance of Accountable Entities in Case-Mix Adjusted Mean EQ-5D Change

![Graph showing performance of accountable entities in case-mix adjusted mean EQ-5D change](image)

- **NHS trusts**
- **99.8% confidence limits**
- **Independent sector hospitals**
- **95% confidence limits**
Example: Post-Prostatectomy Quality Assessment
(Courtesy, Andrew Vickers)

56 years old, 19 months since surgery
Current PSA: <0.05

Pathology
Gleason 3 + 4  Organ confined  PSA Before Surgery: 1.69

Alert
- Erectile dysfunction. 1st Alert.
- Urinary dysfunction > 1 yr after surgery. 1st Alert

Surveys
Most Recent Survey: Wednesday, March 02, 2011. 5 weeks ago

Erectile function
- Baseline Score (Physician): 4
- Baseline Score (Patient): 29 / 30 (Good)
- Current Erection sufficient MOST TIMES
- Current Score: 20 / 30 (Intermediate)

Urinary function
- Baseline Score (Physician): 2
- Baseline Score (Patient): 21 / 21 (Good)
- Current: 1 pad per day
- Current Score: 18 / 21 (Good)

Bowel function
- No bowel symptoms

Quality of life
- Current Score: 6 / 10
Current ASCO Initiative

• Develop cancer-specific PRO-PMs adhering to NQF endorsement criteria for use in Quality Oncology Practice Initiative (QOPI) Program

• Initial areas:
  – Post-chemotherapy nausea
  – Pain control with advanced/metastatic disease
Automated Symptom Alerts Reduce Postoperative Symptom Severity After Cancer Surgery: A Randomized Controlled Clinical Trial


ABSTRACT

Purpose
Patients receiving cancer-related thoracotomy are highly symptomatic in the first weeks after surgery. This study examined whether at-home symptom monitoring plus feedback to clinicians about severe symptoms contributes to more effective postoperative symptom control.

Patients and Methods
We enrolled 100 patients receiving thoracotomy for lung cancer or lung metastasis in a two-arm randomized controlled trial; 79 patients completed the study. After hospital discharge, patients rated symptoms twice weekly for 4 weeks via automated telephone calls. For intervention group patients, an e-mail alert was forwarded to the patient’s clinical team for response if any of a subset of symptoms (pain, disturbed sleep, distress, shortness of breath, or constipation) reached a predetermined severity threshold. No alerts were generated for controls. Group differences in...
Abstract

Purpose: The use of electronic patient-reported outcomes (PRO) systems is increasing in cancer clinical care settings. This review comprehensively identifies existing PRO systems and explores how systems differ in the administration of PRO assessments, the integration of information into the clinic workflow and electronic health record (EHR) systems, and the reporting of PRO information.

Methods: Electronic PRO (e-PRO) systems were identified through a semistructured review of published studies, gray literature, and expert identification. System developers were contacted to provide detailed e-PRO system characteristics and clinical implementation information using a structured review form.

Results: A total of 33 unique systems implemented in cancer clinical practice were identified. Of these, 81% provided detailed information about system characteristics. Two system classifications were established: treatment-centered systems designed for patient monitoring during active cancer treatment (n = 8) and patient-centered systems following patients across treatment and survivorship periods (n = 19). There was little consensus on administration, integration, or result reporting between these system types. Patient-centered systems were more likely to provide user-friendly features such as at-home assessments, integration into larger electronic system networks (eg, EHRs), and more robust score reporting options. Well-established systems were more likely to have features that increased assessment flexibility (eg, location, automated reminders) and better clinical integration.

Conclusion: The number of e-PRO systems has increased. Systems can be programmed to have numerous features that facilitate integration of PRO assessment and routine monitoring into clinical care. Important barriers to system usability and widespread adoption include assessment flexibility, clinical integration, and high-quality data collection and reporting.
Conclusions

• PROs reflect the patient experience
• Measurement science in PROs is mature in clinical trials, but nascent in CER, quality assessment, and clinical care
• Limited work in surgical settings
• Multiple collaborative and funding opportunities

Contact: Ethan Basch: ebasch@med.unc.edu