Introduction to Patient Reported Outcomes

Introduction to Clinical Research:
A Two-week Intensive Course
July 19, 2011

Milo Puhan, MD, PhD, Associate Professor
Patient-reported outcomes (PRO) is a broad group of outcomes that directly reflect the patients’ perspective on symptoms, functional impairment and health-related quality of life.

The development of any PRO instrument should follow a transparent process from the conceptual framework to the testing of measurement properties.

PRO instruments should be selected based on their measurement properties, knowledge about their interpretation and the existing literature.
What do patient report outcomes (PRO) measure?
Definition of patient-reported outcomes

Information about a feature of health/disease that is obtained directly from the patient (with no interpretation by anyone else)
PROs: from simple to very complex measurements

- Multi-item
  - Multipe domains

- Measurement Complexity
  - Single Item
    - Dyspnea when walking
    - Fatigue
    - Pain during daily activities
    - Pain during exercise

- Abstractness of outcome
  - Social Activities
  - Activities of Daily Living
  - Physical Function
  - Symptom Index
  - Health-related quality of life
Patient-reported outcomes: Symptoms

Uni-dimensional

Dyspnea associated with physical activity

Medical Research Council dyspnea scale

<table>
<thead>
<tr>
<th>Grade</th>
<th>Degree of breathlessness related to activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Not troubled by breathlessness except on strenuous exercise</td>
</tr>
<tr>
<td>2</td>
<td>Short of breath when hurrying or walking up a slight hill</td>
</tr>
<tr>
<td>3</td>
<td>Walks slower than contemporaries on level ground because of breathlessness, or has to stop for breath when walking at own pace</td>
</tr>
<tr>
<td>4</td>
<td>Stops for breath after walking about 100m or after a few minutes on level ground</td>
</tr>
<tr>
<td>5</td>
<td>Too breathless to leave the house, or breathless when dressing or undressing</td>
</tr>
</tbody>
</table>
**Patient-reported outcomes: Symptoms**

**Multi-dimensional**

Dyspnea in different situations

### Chronic Respiratory Questionnaire dyspnea domain

<table>
<thead>
<tr>
<th>Activity</th>
<th>Extremely short of breath</th>
<th>Very short of breath</th>
<th>Quite a bit short of breath</th>
<th>Moderate shortness of breath</th>
<th>Some shortness of breath</th>
<th>A little shortness of breath</th>
<th>Not at all short of breath</th>
<th>Not Done</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Feeling emotional such as angry or upset</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>2 Taking care of your basic needs (bathing, showering, eating or dressing)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>3 Walking</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>4 Performing chores (such as housework, shopping, groceries)</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>5 Participating in social activities</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td>6</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

→ **Summary dyspnea domain score**
Patient-reported outcomes: Functional impairment

Uni-dimensional

<table>
<thead>
<tr>
<th>How many times a week do you usually do:</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) 20 minutes or more of vigorous-intensity physical activity that makes you sweat or puff and pant (for example, heavy lifting, digging or jogging)?</td>
</tr>
<tr>
<td>0 1 2 3 4 5 6 7+ times</td>
</tr>
</tbody>
</table>

Multi-dimensional

Questionnaires with multiple questions
(e.g. Minnesota leisure time physical activity questionnaire)
Patient-reported outcomes: Health-related quality of life

- Security
- Economy
- Political stability
- Social environment
- Infrastructure

Health

Example: Mercer-Studies

Symptoms

Health-related quality of life

- Physical functioning
- Mental functioning

Example: SF-36
Patient-reported outcomes: Health-related quality of life

Physical functioning
- House keeping
- Walking
- Doing sports

Symptoms
- Pain
- Dyspnea
- Fatigue

Mental functioning
- Depression
- Anxiety

→ Questions do not address directly “quality of life”
→ Abstract construct derived from underlying questions
Uni-dimensional

Please indicate on the scale from 0 to 100 how your health state was during last 7 days.
Patient-reported outcomes: Health-related quality of life

SF-36

36 questions

8 domains

- Physical function
- Role physical
- Bodily pain
- General Health
- Vitality
- Social function
- Role emotional
- Mental Health

2 summary scores

- Physical component score
- Mental component score
Patient-reported outcomes: Health-related quality of life

Disease-specific instruments: *Chronic Respiratory Questionnaire*

20 questions

- Dyspnea
- Fatigue
- Emotional function
- Mastery

4 domains

Total score
PROs: from simple to very complex measurements

- Symptom Index
- Pain
- Fatigue
- Dyspnea during daily activities
- Pain during exercise
- Dyspnea when walking
- Physical Function
- Activities of Daily Living
- Social Activities
- Health-related quality of life
Development of PROs
The development of PROs is iterative

i. Identify Concepts and Develop Conceptual Framework
- Identify concepts and domains that are important to patients.
- Determine intended population and research application.
- Hypothesize expected relationships among concepts.

ii. Create Instrument
- Generate items.
- Choose administration method, recall period, and response scales.
- Draft instructions.
- Format instrument.
- Draft procedures for scoring and administration. Pilot test draft instrument. Refine instrument and procedures.

iii. Assess Measurement Properties
- Assess score reliability, validity, and ability to detect change.
- Evaluate administrative and respondent burden. Add, delete, or revise items.
- Identify meaningful differences in scores. Finalize instrument formats, scoring, procedures, and training materials.

iv. Modify Instrument
- Change concepts measured, populations studied, research application, instrumentation, or method of administration.
Is there a specific conceptual framework?

A valid PRO should be based on a conceptual framework, which includes:

- **What is the target population?**
  - Any disease?
  - Specific disease?
  - Disease severity?
  - Clinical or general population?

- **What should be measured?**
  - Symptoms?
  - Functional impairment?
  - Health-related quality of life?

- **What’s the purpose of the instrument?**
  - Treatment evaluation?
  - Comparison of patients?
  - Prediction of outcomes?
  - evaluative
  - discriminative
  - predictive
Conceptual framework

**Concept**
CRQ: COPD-specific health-related quality of life

**Domains**
- Dyspnea
- Fatigue
- Emotional function
- Mastery

**Subdomains**

**Items**
“Dyspnea when doing chores”
Answer options: Likert-type 1-7
Scores: 1-7 per domain
Recall period: 2 weeks
Steps in the development of PROs

1. Conceptual framework
2. A priori considerations
3. Item and domain identification
4. Item selection
5. Questions
6. Answer options
7. Pilot testing
8. Revision
9. Testing of measurement properties (validation)
10. Adaptation
11. Translations
12. Validation on other populations
Translation of PROs

Testing of measurement properties (validation)

Translations

Forward Translation 1

Forward Translation 2

Professional interpreters

Consensus meeting

Professional interpreters
Clinicians
Methodologists

Translated version 1

Pilot testing

Translated version 2

Back translation

Revision

Validation

Pilot testing
Measurement formats and properties
Relevant properties of any measurement

Repeatability  →  Reproducibility

Internal consistency  →  Inter-item correlations within domains

Validity  →  Measures what is intended to be measured

Responsiveness  →  Detects changes over time

“Objective” vs “subjective” irrelevant → look at empirical evidence about measurement properties
Reliability and validity

Poor reliability and validity

Good reliability but poor validity

Good reliability and validity
**Test-retest reliability**

First administration

Second administration

Typically 1-2 weeks)

No change (treatments, exacerbations)

Inappropriate statistic

Not bad, but does not correct for systematic differences

Adequate

Intra-class correlation coefficient

Between person variance

Between + within person variance

$r = 0.9$
The validity challenge: No gold standard

- Face validity (expert knowledge) considered insufficient
- Known-group validity: Expected versus observed distributions
  
  ![Diagram showing dyspnea severity versus disease severity]
  
  **Dyspnea**
  
  - Extreme
  - Moderate
  - No

  **Severity of disease**
  
  - Mild
  - Moderate
  - Severe

- Construct validity: Expected versus observed correlations with external validation instruments
## Construct validity: Expected versus observed correlations

<table>
<thead>
<tr>
<th>Instrument</th>
<th>Chronic Respiratory Questionnaire</th>
</tr>
</thead>
<tbody>
<tr>
<td>Validation instruments</td>
<td>Dyspnea</td>
</tr>
<tr>
<td>MRC Dyspnea scale</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Self-reported physical activity</td>
<td>Mastery</td>
</tr>
<tr>
<td>Six-minute walk distance</td>
<td>Emotional function</td>
</tr>
<tr>
<td>Exacerbations</td>
<td></td>
</tr>
<tr>
<td>SF-36 physical functioning</td>
<td></td>
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<tr>
<td>SF-36 mental functioning</td>
<td></td>
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<tr>
<td>Hospital Anxiety and Depression Scale</td>
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### Construct validity: Expected correlations

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<td><strong>MRC Dyspnea scale</strong></td>
<td></td>
</tr>
<tr>
<td>High (&gt;0.5)</td>
<td>Moderate (0.3-0.5)</td>
</tr>
<tr>
<td>Moderate (0.3-0.5)</td>
<td>Moderate (0.3-0.5)</td>
</tr>
<tr>
<td>Low (&lt;0.3)</td>
<td></td>
</tr>
<tr>
<td><strong>Self-reported physical activity</strong></td>
<td></td>
</tr>
<tr>
<td>Moderate (0.3-0.5)</td>
<td>High (&gt;0.5)</td>
</tr>
<tr>
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</tr>
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<td>Moderate (0.3-0.5)</td>
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</tr>
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<td><strong>Validation instruments</strong></td>
<td>Dyspnea</td>
</tr>
<tr>
<td>MRC Dyspnea scale</td>
<td>0.62</td>
</tr>
<tr>
<td></td>
<td>(&gt;0.5)</td>
</tr>
<tr>
<td>Self-reported physical activity</td>
<td>0.40</td>
</tr>
<tr>
<td></td>
<td>(0.3-0.5)</td>
</tr>
<tr>
<td>Six-minute walk distance</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>(0.3-0.5)</td>
</tr>
<tr>
<td>Exacerbations</td>
<td>0.38</td>
</tr>
<tr>
<td></td>
<td>(0.3-0.5)</td>
</tr>
<tr>
<td>SF-36 physical functioning</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
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</tr>
<tr>
<td>SF-36 mental functioning</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>(&lt;0.3)</td>
</tr>
<tr>
<td>Hospital Anxiety and Depression Scale</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>(&lt;0.3)</td>
</tr>
</tbody>
</table>
Responsiveness: Expected versus observed change

First administration

Treatment of known effectiveness

Second administration

Dyspnea

Exacerbation (recovery)

Baseline

Follow-up

Extreme

No

Beginning

Peak

Recovery

Exacerbations
The minimal important difference
How should we interpret these data?

Respiratory rehabilitation vs usual care for COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Difference CRQ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simpson K 1992</td>
<td>0.69 (-0.2-1.57)</td>
</tr>
<tr>
<td>Goldstein 1994</td>
<td>0.52 (0.14-0.91)</td>
</tr>
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<td>Güell 1995</td>
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<td>0.70 (0.3-1.1)</td>
</tr>
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<td>White 2002</td>
<td>0.17 (-0.1-0.44)</td>
</tr>
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<td>Oh Eg 2003</td>
<td>0.95 (0.36-1.54)</td>
</tr>
<tr>
<td>Singh V 2003</td>
<td>0.83 (0.04-1.61)</td>
</tr>
<tr>
<td>Faager 2004</td>
<td>0.34 (-0.36-1.34)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.54 (0.391-0.702, p&lt;0.001)</td>
</tr>
</tbody>
</table>
Imagine the following results

<table>
<thead>
<tr>
<th>Difference CRQ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.54 (0.391-0.702, p&lt;0.001)</td>
</tr>
<tr>
<td>0.44 (0.291-0.602, p&lt;0.001)</td>
</tr>
<tr>
<td>0.34 (0.191-0.502, p&lt;0.001)</td>
</tr>
<tr>
<td>0.24 (0.091-0.402, p=0.01)</td>
</tr>
<tr>
<td>0.14 (0.00-0.302, p=0.05)</td>
</tr>
<tr>
<td>0.04 (-0.191-0.202, p=0.25)</td>
</tr>
</tbody>
</table>

We need a quantitative interpretation
"the smallest difference in the outcome of interest that informed patients or their proxies perceive as important and that may lead to a change in the management"
The MID of the CRQ is 0.5

Effects of inhaled drugs

<table>
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</table>
## Methods to determine the MID

<table>
<thead>
<tr>
<th>Consensus-based</th>
<th>Distribution-based</th>
<th>Anchor-based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Experts reach a consensus (e.g. Delphi methods)</td>
<td>Statistical criteria: How strong is signal compared to noise</td>
<td>External instrument (anchor) with known MID used to estimate MID</td>
</tr>
<tr>
<td></td>
<td>Standardized response mean $\geq 0.5$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cohen’s effect size $\geq 0.5$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standard error of measurement</td>
<td></td>
</tr>
</tbody>
</table>
### Table 2: Anchor-based method to determine the minimal important difference of the HADS

<table>
<thead>
<tr>
<th>Change in HADS anxiety score</th>
<th>Regression equation</th>
<th>Corresponding to 0.5 change in CRQ score (95% confidence interval*)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.73 + 1.35*CRQemotional function, ( r^2 = 0.30 )</td>
<td>1.41  (1.18–1.63)</td>
</tr>
<tr>
<td></td>
<td>1.04 + 1.05*CRQmastery, ( r^2 = 0.26 )</td>
<td>1.57  (1.37–1.76)</td>
</tr>
<tr>
<td>Change in HADS total score</td>
<td>1.07 + 1.21*CRQemotional function, ( r^2 = 0.31 )</td>
<td>1.68  (1.48–1.87)</td>
</tr>
<tr>
<td></td>
<td>1.00 + 1.20*CRQtotal, ( R^2 = 0.26 )</td>
<td>1.60  (1.38–1.82)</td>
</tr>
</tbody>
</table>
Between 1.41 and 1.68 with anchor-based method

Between 1.17 and 1.40 with distribution-based method

→ 1.5 on scale from 0-21 seems fair estimate

→ Always use different methods since none of them is perfect
Selection of instruments
PROs: What are you interested in?

- Pain
- Fatigue
- Dyspnea during daily activities
- Pain during exercise
- Dyspnea when walking
- Symptom Index
- Physical Function
- Activities of Daily Living
- Social Activities
- Health-related quality of life

Measurement Complexity

Multi-item
- Multiple domains

Single Item

Abstractness of outcome
**ProQolid, the Patient-Reported Outcome and Quality of Life Instruments Database**

**About ProQolid**

Developed by Mapi Research Institute and managed by Mapi Research Trust (Lyon, France), ProQolid aims to identify and describe PRO and QOL instruments to help you choose appropriate instruments and facilitate your access to them.

**Free access**

This level is available to all ProQolid visitors at no charge. For each instrument in the database, you will find 14 categories of basic information (e.g., author, objective, mode of administration, original language, existing translations, pathology, number of items, etc.).

**Advanced access (members only)**

This level presents a greater degree of practical information on each instrument, most notably the author’s details and contact information, conditions of use, psychometric properties, etc., and, when available, a review copy of the original instrument, its translations, and a user manual.

**Highlights**

- **ProQolid Demo**
- **Health and Quality of Life Outcomes’s article on ProQolid**
- **ISOQOL members discount on ProQolid subscriptions**
- **We’re proud to include**
  - the US FDA, the Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (IQWIG)
  - the National Institute of Health (NIH) among our growing list of ProQolid subscribers

**Database**

**ProQolid currently contains**

- Descriptions of 647 instruments
- 500 review copies of original instruments
- Review copies of 1010 translations
- Review copies of 170 user manuals
- Descriptions of 82 databases

**On-going developments**

Include

- 26% of the seventh update of the instruments described in the database in collaboration with their developers completed
- New information added for each instrument: Complete description of the methodology of development
- 6 new instruments added in 2009

**Instruments recently added**

- Standard Evaluation Questionnaire on Pain (SEQ Pain)
- Urinary Symptom Profile (USP)
- QUALIVEEN 30 items (QUALIVEEN-30)
- More

**NB:** ProQolid content is based on information collected in the literature and/or validated by the authors of the instruments. The adequacy of study methodology and psychometric properties is not evaluated.

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Have standard steps for the development been followed?

- Conceptual framework
  - A priori considerations
    - Item and domain identification
      - Item selection
        - Questions
          - Answer options
            - Pilot testing
              - Revision
                - Testing of measurement properties (validation)
                  - Adaptation
                    - Translations
                      - Validation on other populations
Choice of patient-reported outcomes for CER

Symptoms, functioning or health-related quality of life?

Ideally **matches measures of existing trials** → Meta-analysis!

Can be **measured reliably**

**Responsive to change** → disease-specific instruments

Established **MID** using valid methods

Is **reasonably efficient to measure** (budget considerations)
Planning of a CER study in COPD

Trial of rehabilitation in patients with COPD

<table>
<thead>
<tr>
<th>Our considerations</th>
<th>MRC dyspnea scale</th>
<th>SF-36</th>
<th>CRQ</th>
<th>St Georges Resp Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interested in health-related quality of life</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Matches measures of existing trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Can be measured reliably</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Responsive to change</td>
<td></td>
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<tr>
<th>Our considerations</th>
<th>MRC dyspnea scale</th>
<th>SF-36</th>
<th>CRQ</th>
<th>St Georges Resp Q</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interested in health-related quality of life</td>
<td></td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Matches measures of existing trials</td>
<td>-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Can be measured reliably</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Responsive to change</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+/-</td>
</tr>
<tr>
<td>Established MID</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Efficient to measure</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
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</table>
Patient-reported outcomes (PRO) is a broad group of outcomes that directly reflect the patients’ perspective on symptoms, functional impairment and health-related quality of life.

The development of any PRO instrument should follow a transparent process from the conceptual framework to the testing of measurement properties.

PRO instruments should be selected based on their measurement properties, knowledge about their interpretation and the existing literature.