To Combine or Not Combine: Individual Symptom Scores Versus Summary Scores

Moderator:
Margaret L. Rothman, PhD

Panelists:
Charles S. Cleeland, PhD
Donald L. Patrick, PhD, MSPH
Ruyi He, MD
Rima Izem, PhD
Opening Remarks and Introductions

Moderator:
Margaret L. Rothman, PhD
Johnson & Johnson Pharmaceutical Services, LLC
Symptom Measures in Cancer

Charles S. Cleeland
UT MD Anderson Cancer Center

SECOND ANNUAL PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

March 15, 2011 ■ Silver Spring, MD

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Two Questions

• How does a single-item pain measure compare with a pain scale with high internal reliability?
  Longitudinal data on breast cancer patients, responding to the Brief Pain Inventory (BPI) and the M. D. Anderson Symptom Inventory (MDASI) (Shi, unpublished data)

• How might one construct a composite symptom score for patients with lung cancer?
  Longitudinal data on three cohorts of patients with lung cancer being treated with surgery (early stage), chemoradiotherapy (mid stage), or chemotherapy (late stage), using the MDASI Lung Cancer Module (Mendoza et al, 2011)
Single Pain Item vs. Pain Scale

- “Pain worst” rating from BPI
- Pain severity subscale from the BPI (four items: worst, least, average and now, $\alpha \sim .9$)
- Single item “pain worst” rating from the MDASI
- Context: Patients with breast cancer beginning aromatase inhibitor adjuvant therapy
- Measurement: monthly
  - Baseline paper-and-pencil
  - Subsequent measures by interactive voice response system
Congruity of Scales
Breast Cancer

Severity, 0–10 Scale

Month

BPI pain scale
MDASI pain worst
BPI pain worst
## Test-Retest Reliability

### Correlation coefficients between BPI pain scale and MDASI pain worst

<table>
<thead>
<tr>
<th></th>
<th>Month 0</th>
<th>Month 3</th>
<th>Month 6</th>
<th>Month 9</th>
<th>Month 12</th>
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<tr>
<td>$r$</td>
<td>0.805</td>
<td>0.789</td>
<td>0.887</td>
<td>0.948</td>
<td>0.950</td>
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<tr>
<td>$P$</td>
<td>&lt;.0001</td>
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### Intraclass correlation (ICC) of month 3 and 4

<table>
<thead>
<tr>
<th></th>
<th>ICC (95% CI)</th>
<th>Mean (SD)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td><strong>Month 3</strong></td>
<td><strong>Month 4</strong></td>
</tr>
<tr>
<td>BPI pain scale</td>
<td>0.824 (0.689 – 0.903)</td>
<td>1.61 (1.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.73 (1.85)</td>
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<tr>
<td>MDASI pain worst</td>
<td>0.819 (0.681 – 0.901)</td>
<td>2.15 (2.38)</td>
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<tr>
<td></td>
<td></td>
<td>2.30 (2.20)</td>
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</tbody>
</table>
Single Item vs. Scale

- A single item rating pain as part of multi-symptom assessment performs in a similar fashion compared with a multi-item pain severity scale with strong internal reliability.

- In lieu of calculating internal reliability, other measures of over-time performance (e.g., test-retest) may be used to support the reliability of single items.
Developing a Composite Symptom Score: Three Approaches

From the MDASI Lung Cancer Module (16 symptoms, Mendoza et al, 2011)

• The mean of the most severe symptoms at baseline ("disease based")

• Those items most influencing report of symptom interference ("anchor based")

• First component of a principle components analysis
### Baseline Symptoms
**All Cohorts (N=365)**

<table>
<thead>
<tr>
<th>Top 5</th>
<th>Interference-Based</th>
<th>All Items</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue</td>
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<td>Coughing</td>
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<td>Pain</td>
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<td></td>
<td></td>
<td>Shortness of breath</td>
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</table>
Baseline Symptoms
Surgery (N=85)
Baseline Symptoms
Chemoradiation (N=52)

<table>
<thead>
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<td>Nausea</td>
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<td></td>
<td></td>
<td>Vomiting</td>
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</table>
Baseline Symptoms
Chemoradiation (N=52)

Severity, 0–10 Scale

Week
## Baseline vs. Peak of Therapy Chemoradiation (N=52)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>% Moderate to Severe</th>
<th>At Peak (~Day 42)</th>
<th>% Moderate to Severe</th>
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<tr>
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<td>Fatigue</td>
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<td>Pain</td>
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<td>Distress</td>
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<tr>
<td>Dry mouth</td>
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<tr>
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<td>Vomiting</td>
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<td>Difficulty remembering</td>
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<tr>
<td>Vomiting</td>
<td>0</td>
<td>Numbness</td>
<td>10</td>
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Baseline Symptoms
Chemotherapy (N=185)

<table>
<thead>
<tr>
<th>Top 5</th>
<th>Interference-Based</th>
<th>All Items</th>
</tr>
</thead>
<tbody>
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<td>Lack of appetite</td>
<td>Fatigue</td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>Fatigue</td>
<td>Pain</td>
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<td>Disturbed sleep</td>
<td>Dry mouth</td>
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<td>Nausea</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vomiting</td>
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</table>
Lung Symptoms
Chemotherapy (N=185)

Severity, 0–10 Scale

Week

Top 5
Interference-based
All 14
Coughing
## Baseline vs. End of Cycle 2
### Chemotherapy (N=185)

<table>
<thead>
<tr>
<th>Baseline</th>
<th>% Moderate to Severe</th>
<th>End of Cycle 2</th>
<th>% Moderate to Severe</th>
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<tr>
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<td>Dry mouth</td>
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<tr>
<td>Vomiting</td>
<td>3</td>
<td>Vomiting</td>
<td>7</td>
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</tbody>
</table>
Summary

• Three different approaches to a “symptom composite” for lung cancer yield similar results

• These composites are sensitive to both disease stage and treatment effects

• The utility of these composite measures as endpoints has yet to be tested
Acknowledgments

• Tito R. Mendoza, PhD
  – Associate Professor
• Qiuling Shi, MD, PhD
  – Assistant Professor
• Brad J. Barney, MS
  – Doctoral Student, Biostatistics
• Kai-Ping (Eric) Liao, PhD, MHA
  – Senior Data Analyst
Symptom Assessment in FDA Medical Product Labeling

Donald L. Patrick, PhD, MSPH
University of Washington

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Outline

• Issues
  – From claim to concept to instrument to scores
  – Single item versus multiple item composite scores
  – Unidimensionality of symptom scores
  – Interpretation of single items and composite scores

• Case Examples
  – Cystic Fibrosis Respiratory Symptom Diary
    acknowledgement to Goss and Colleagues
  – EXACT-PRO
    acknowledgement to Kline Leidy and Colleagues
Developed CF Respiratory Symptom Diary (CFRSD)

8 Symptoms items:
- Cough
- Chest tightness
- Difficulty breathing
- Wheeze
- Coughing up mucous
- Fevers and chills
- Fatigue

4 Activity impacts items:
- Impact sleep, school or work attendance
- Causing reduction of usual activities
- Spending more time sitting or lying down

4 Emotional impacts items:
- Worry
- Frustration
- Feeling sad or depressed
- Feeling cranky

From Claim to Concept to Instrument to Score

• Product x improves respiratory symptoms in adults with cystic fibrosis
• Product x improves cough and difficulty breathing in adults with cystic fibrosis
• “Symptoms” to CFRSD to Composite Score or number of symptoms
• “Cough and difficulty breathing” to CFRSD to 2 item or single item profile scores
Results of Factor Analysis

- Project Breath
- Initial Eigen Values > 1.0

- 3 Factors (13 symptoms)
  1. Tired, chills or sweats, sleeping difficulty, worried, cranky, sad, frustrated
  2. Difficulty breathing, cough, cough up mucus, chest tightness, wheeze
  3. Fever
Potential Applications

- Respiratory symptoms alone perform the best
- Counting symptoms alone performs well
- Factor analysis indicates single factor in respiratory symptoms
- Match of medical product objective with CFRSD score
- Which score depends on characteristics and objectives of treatment
23 symptom items identified from patient interviews reduced to 14 following item-level and RASCH analysis

Post-hoc EFA revealed one dominant factor with three domains (breathlessness, cough and sputum, chest symptoms) that accounted for 68% of the variance.
Potential Applications

• Unidimensionality demonstrated but domain scores exist
• Overall composite or domain scores
• Evidence currently for COPD exacerbations only
Measurement Issues

• Do all the symptoms in a symptom composite score move together?
• Do all medical products affect all symptoms?
• Different applications may use different scores
Conclusions

• Single item, domain score, or overall composite scores may be appropriate

• Medical product and claim is overall context

• Evidence of unidimensionality and “moving together” important when using composite scores
Path Forward for IBS Drug Development

Ruyi He, M.D.
Medical Team Leader
Division of Gastroenterology Products
CDER/FDA

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Previously or Currently
FDA-Approved Drugs for IBS

• Lotronex – Severe IBS-D
  • REMS with Elements to Assure Safe Use:
    – Sticker and training program
    – Based on safety issue of ischemic colitis and serious complications of constipation

• Zelnorm – Chronic Idiopathic Constipation and IBS-C
  • Withdrawn because of serious adverse events

• Amitiza – Chronic idiopathic Constipation and IBS-C
<table>
<thead>
<tr>
<th>Product and Specific Indication</th>
<th>Primary Endpoint</th>
<th>Questions Used to Assess Endpoint</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alosetron — IBS-D$^1$</td>
<td>Adequate relief</td>
<td>In the past 7 days, have you had adequate relief of your IBS pain or discomfort?</td>
<td>Binary endpoint (Yes/No)</td>
</tr>
<tr>
<td>Tegaserod — IBS-C$^2$</td>
<td>Satisfactory relief</td>
<td>Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS?</td>
<td>Binary endpoint (Yes/No)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did you have satisfactory relief of your overall IBS symptoms during the last week?</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Did you have satisfactory relief of your abdominal discomfort or pain during the last week?</td>
<td></td>
</tr>
<tr>
<td>Lubiprostone — IBS-C$^3$</td>
<td>Subject Global Assessment of Relief (SGA)</td>
<td>Please consider how you felt during the past treatment period in regard to your IBS, in particular your overall well-being, and symptoms of abdominal pain/discomfort and altered bowel habit.</td>
<td>5-Point Likert scale: worse, not at all relieved, somewhat relieved, considerably relieved, completely relieved</td>
</tr>
<tr>
<td></td>
<td>Modified version of the SGA</td>
<td>How would you rate your relief of IBS symptoms (abdominal discomfort/pain, bowel habits, and other IBS symptoms) over the past week compared with how you felt before you entered the study?</td>
<td>7-Point Likert scale: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, substantially improved</td>
</tr>
</tbody>
</table>
Adequate Relief
Content Validity Issues

Adequate:

• Interpreted inconsistently
• Fails to quantify baseline severity (mild, moderate, severe)
• Fails to quantify treatment effect (minimal improvement vs. complete resolution)
• Fails to capture worsening symptoms
Adequate Relief
Content Validity Issues

Relief:

• Interpreted inconsistently

• Refers to a comparison of present to some unspecified time in past

• Binary response: yes/no
  • Does not quantify response or absence of symptoms
Challenges to Adequately Defining IBS Symptoms

• Symptoms are chronic but intermittent
• Intra-subject symptom variability (e.g. IBS-D patients may experience constipation as well as diarrhea)
• Inter-subject symptom variability
• Determining content valid terminology that can adequately measure signs/symptoms
  – Abdominal pain versus abdominal discomfort
Issues with Patient Ratings of Change as Primary Endpoints

• A single item does not measure which symptoms the patient experiences at baseline
• A single item does not measure which symptoms change with treatment
  – Cannot define which symptoms improve and which symptoms worsen
Evolution of IBS Primary Endpoints

Previously used primary endpoints in IBS clinical trials
• Inadequate single-item patient ratings of change
• Did not adequately capture IBS signs/symptoms

Ideal primary endpoints
• Patient-reported outcome measure of all of the clinically important signs/symptoms of IBS
• Currently not available
Guidance for Industry
Irritable Bowel Syndrome —
Clinical Evaluation of
Products for Treatment

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the Federal Register of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Ruyi He at 301-796-0910 or Ann Marie Trentacosti at 770-716-9984.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

March 2010
Clinical/Medical
IBS-Constipation

Proposed Primary Endpoints

Patient should be a weekly responder in BOTH pain severity AND stool frequency

- **Pain Severity Responder**
  - Decrease in weekly average of “worst pain in past 24 hours” score of \( \geq 30\% \)

- **Stool Frequency Responder**
  - An increase of at least 1 complete spontaneous bowel movement (CSBM) per week from baseline
IBS-Diarrhea

Proposed Primary Endpoints

Patient should be a weekly responder in BOTH pain severity AND stool consistency

• Pain Severity Responder
  – Decrease in weekly average of “worst pain in past 24 hours” score of ≥ 30%

• Stool Consistency Responder
  – Patient who experiences a ≥50% reduction in the number of days per week with at least one stool which has a consistency of ≥ type 6 compared with baseline
Summary

• DGP and SEALD are working together to provide a path forward for IBS drug development

• IBS Draft Guidance provides recommendations about interim clinical trial endpoints until content valid and reliable instruments of IBS signs and symptoms becomes available for use in clinical trials

• The PRO Consortium IBS Working Group is working to develop adequate measures of IBS signs/symptoms
Acknowledgments

• Ann Marie Trentacosti, MD
  – Medical Team Leader, SEALD, CDER/FDA
• Laurie Burke, RPh, MPH
  – Director, SEALD, CDER/FDA
• Donna Griebel, MD
  – Director, DGP, CDER/FDA
Multi-items PRO
Statistical Considerations

Rima Izem
FDA/CDER/OB/DB4

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Main Points

• Multi-items PRO are composite variables measuring one construct

• Tracking each item in multi-items PRO is important

• Multiple claims from a multi-items PRO, dilemma?
Multi-items PRO

- **Multi-items PRO** = multiple questions
  - → one endpoint/score
  - → 1 labeling claim

Ex:
CFQR-Respiratory = Q. cough, wheezing and sputum
  - → total score = sum scores
  - → improvement of respiratory symptoms in Cystic Fibrosis (CF) patients
Multi-items PRO as composite variable

• From ICH-E9 (1998) on composite variable: “If a single primary variable cannot be selected from multiple measurements associated with the primary objective, another useful strategy is to integrate or combine the multiple measurements into a single or composite variable, using a predefined algorithm. Indeed, the primary variable sometimes arises as a combination of multiple clinical measurements (e.g., the rating scales used in arthritis, psychiatric disorders, and elsewhere)”
Multi-items PRO, one construct

- Paradox? One construct and multiple items

- ICH-E9 (1998): When a rating scale is used as a primary variable, it is especially important to address factors such as content validity [..], inter- and intra-rater reliability [..], and responsiveness for detecting changes in the severity of disease.

- PRO guidance (2009): Content validity, Construct Validity, Reliability, Ability to Detect change
Multi-items PRO, scoring

- Binary endpoint.

E.g. Pulmonary exacerbation in Cystic Fibrosis patients (yes/no) using Fuchs or Ramsay et al criteria.

Fuchs: $\geq 4/12$ signs and symptoms

Ramsay et al: $\geq 2/7$ symptoms + $\geq 1/3$ signs
Multi-items PRO, scoring (contd)

• Continuous score:
  – Sum e.g. CFQR-respiratory domain
  – Weighted sum (expert’s weights or data-driven weights)
  – Rasch Analysis (e.g. MSWS-12 item)
  – IRT (e.g. PROMIS work by NIH)
Why track each item?

• Track **trt effect** in each symptom and possible heterogeneities (subgroups, sites,...etc)

• Assess psychometric properties of tools in clinical trial.

• PRO development is iterative: develop tool, use it in clinical trial and **improve** tool

• Disease and therapy change over time (e.g. trt of CF patients over the past decade)
Tracking each item: How? What? Where?

• How? Submitting total score, item scores, psychometric analyses and item by item analyses to FDA

• What? Psychometric properties, trt effect on each item?

• Where? In Statistical Review? In Clinical Review? In the label?
Multi-items PRO and Multiple Claims

Source: PRO Guidance (2009)
Multi-items PRO and Multiple Claims (contd)

• From ICH-E9: When a composite variable is used as a primary variable, the components of this variable may sometimes be analyzed separately, where *clinically meaningful* and validated.
PRO Guidance (2009): A multidomain PRO measure may successfully support a labeling claim based on one or a subset of the domains measured if an *a priori* analysis plan prespecifies the domains that will be targeted as endpoints and the method of analysis that will **adjust for the multiplicity** of tests for the specific claim. The use of domain subsets as clinical trial endpoints presupposes that the PRO instrument was **adequately developed and validated** to measure the subset of domains **independently** from the other domains.
Multi-items and Multiple Claims contd)

- Multiple testing strategies (used in many composite endpoints) can help frame the problem. E.g.
  - Hierarchical closed test,
  - Fall back,
  - Graphical approach (Bretz et al. (2009))
Multi-items PRO and Multiple Claims Dilemma

Possible tension/contradiction with statistical tools showing simultaneously:

– Multiple items $\rightarrow$ 1 dimension or score (validation of 1 concept)

– Multiple items $\rightarrow$ multiple dimensions (each dimension = domain)
In Summary

- Multi-items PRO are *composite* variables measuring *one construct*

- Tracking each item in multi-items PRO is important

- Multiple claims from a multi-items PRO, dilemma?
Acknowledgments

• OB: Lisa Kammerman, Scott Komo

• Seald: Elektra Papadopoulos
Back-up slides
### MSWS-12 item, item by item information

<table>
<thead>
<tr>
<th>MSWS-12 Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Ability to walk</td>
<td>Off Fampridine</td>
</tr>
<tr>
<td></td>
<td>On Fampridine</td>
</tr>
<tr>
<td>2. Ability to run</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td>3. Ability to climb stairs</td>
<td>Extremely</td>
</tr>
<tr>
<td></td>
<td>Extremely</td>
</tr>
<tr>
<td>4. Made standing difficult</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td>5. Limited balance standing or walking</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td>6. Limited walking distance</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Quite a bit</td>
</tr>
<tr>
<td>7. Increased effort needed to walk</td>
<td>Moderate</td>
</tr>
<tr>
<td></td>
<td>Quite a bit</td>
</tr>
<tr>
<td>8. Support walking INDOORS</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td>9. Support walking OUTDOORS</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Quite a bit</td>
</tr>
<tr>
<td>10. Slowed your walking</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Moderately</td>
</tr>
<tr>
<td>11. Affected how smoothly you walk</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Quite a bit</td>
</tr>
<tr>
<td>12. Concentrate on walking</td>
<td>Quite a bit</td>
</tr>
<tr>
<td></td>
<td>Quite a bit</td>
</tr>
</tbody>
</table>

6 items change (order: 1,5,7,8,3,10)

Source: Acorda Back-up Presentation, Slides for the October 14, 2009 Meeting of the Peripheral and Central Nervous System Drugs Advisory Committee, www.fda.gov
Binary multi-items, examples

TABLE 1. DIAGNOSTIC CRITERIA OF A PULMONARY EXACERBATION

Fuchs and colleagues, Pulmozyme:
"Exacerbation of respiratory symptoms": a patient treated with parenteral antibiotics for any 4 of the following 12 signs or symptoms:
- Change in sputum
- New or increased hemoptysis
- Increased cough
- Increased dyspnea
- Malaise, fatigue, or lethargy
- Temperature above 38°C
- Anorexia or weight loss
- Sinus pain or tenderness
- Change in sinus discharge
- Change in physical examination of the chest
- Decrease in pulmonary function by 10% or more from a previously recorded value
- Radiographic changes indicative of pulmonary infection

Ramsey and colleagues, inhaled tobramycin:
Pulmonary exacerbation indicated by at least two of the following seven symptoms during the study:
- Fever (oral temperature >38°C)
- More frequent coughing (increase of 50%)
- Increased sputum volume (increase of 50%)
- Loss of appetite
- Weight loss of at least 1 kg
- Absence from school or work (at least 3 or preceding 7 days) due to illness
- Symptoms of upper RTI

These symptoms had to have been associated with at least one of the following three additional criteria:
- Decrease in FVC of at least 10%
- An increase in respiratory rate of at least 10 breaths/min
- A peripheral blood neutrophil count of ≥15,000/mm³

Binary multi-items, example 2

Improvement in RA

• Tender and swollen joint counts (20% improvement)

AND

• ACR-core set measures: (20% improvement in 3 of the 5 measures)
  – patient global assessment
  – physician global assessment
  – pain
  – disability
  – acute phase reactant
### Table 3: Components of ACR Response in Study I

<table>
<thead>
<tr>
<th>Parameter (median)</th>
<th>Placebo N = 80</th>
<th>ENBREL®a N = 78</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>3 Months</td>
</tr>
<tr>
<td>Number of tender joints b</td>
<td>34.0</td>
<td>29.5</td>
</tr>
<tr>
<td>Number of swollen joints c</td>
<td>24.0</td>
<td>22.0</td>
</tr>
<tr>
<td>Physician global assessment d</td>
<td>7.0</td>
<td>6.5</td>
</tr>
<tr>
<td>Patient global assessment d</td>
<td>7.0</td>
<td>7.0</td>
</tr>
<tr>
<td>Pain d</td>
<td>6.9</td>
<td>6.6</td>
</tr>
<tr>
<td>Disability index e</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>31.0</td>
<td>32.0</td>
</tr>
<tr>
<td>CRP (mg/dL)</td>
<td>2.8</td>
<td>3.9</td>
</tr>
</tbody>
</table>

* Results at 6 months showed similar improvement.

a 25 mg ENBREL® SC twice weekly.
b Scale 0 – 71.
c Scale 0 – 68.
d Visual analog scale; 0 = best, 10 = worst.
e Health Assessment Questionnaire1; 0 = best, 3 = worst; includes eight categories: dressing and grooming, arising, eating, walking, hygiene, reach, grip, and activities.
f p < 0.01, ENBREL® vs. placebo, based on mean percent change from baseline.

Source: ENBREL label
One item PRO

• One item PRO = 1 symptom’s score from a multi-symptoms disease. Ex: Relief of itching in Allergic Conjunctivitis.

• One item PRO = summary of a symptom over time. Ex: Ocular Pain over time after eye surgery.

• **1 item** PRO = 1 question (over time)
  = 1 endpoint/score
  → 1 labeling claim
One item PRO scoring

• Binary endpoint: (yes/no) or (above threshold/below threshold).

• Continuous endpoint.

• Ordinal endpoint...rarely
Multi-items PRO and Multiple Claims

- Scenario: multi-items PRO with one general claim and several smaller claims

- Multi-items = multiple questions
  -> multiple endpoint/scores
  -> 1 general + domains claims