SECOND ANNUAL PATIENT-REPORTED OUTCOME (PRO) CONSORTIUM WORKSHOP

March 15, 2011 ■ Silver Spring, MD

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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

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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cancer patients, responding to the Brief Pain Inventory (BPI) and the M. D. Anderson Symptom Inventory (MDASI) (Shi, unpublished data)

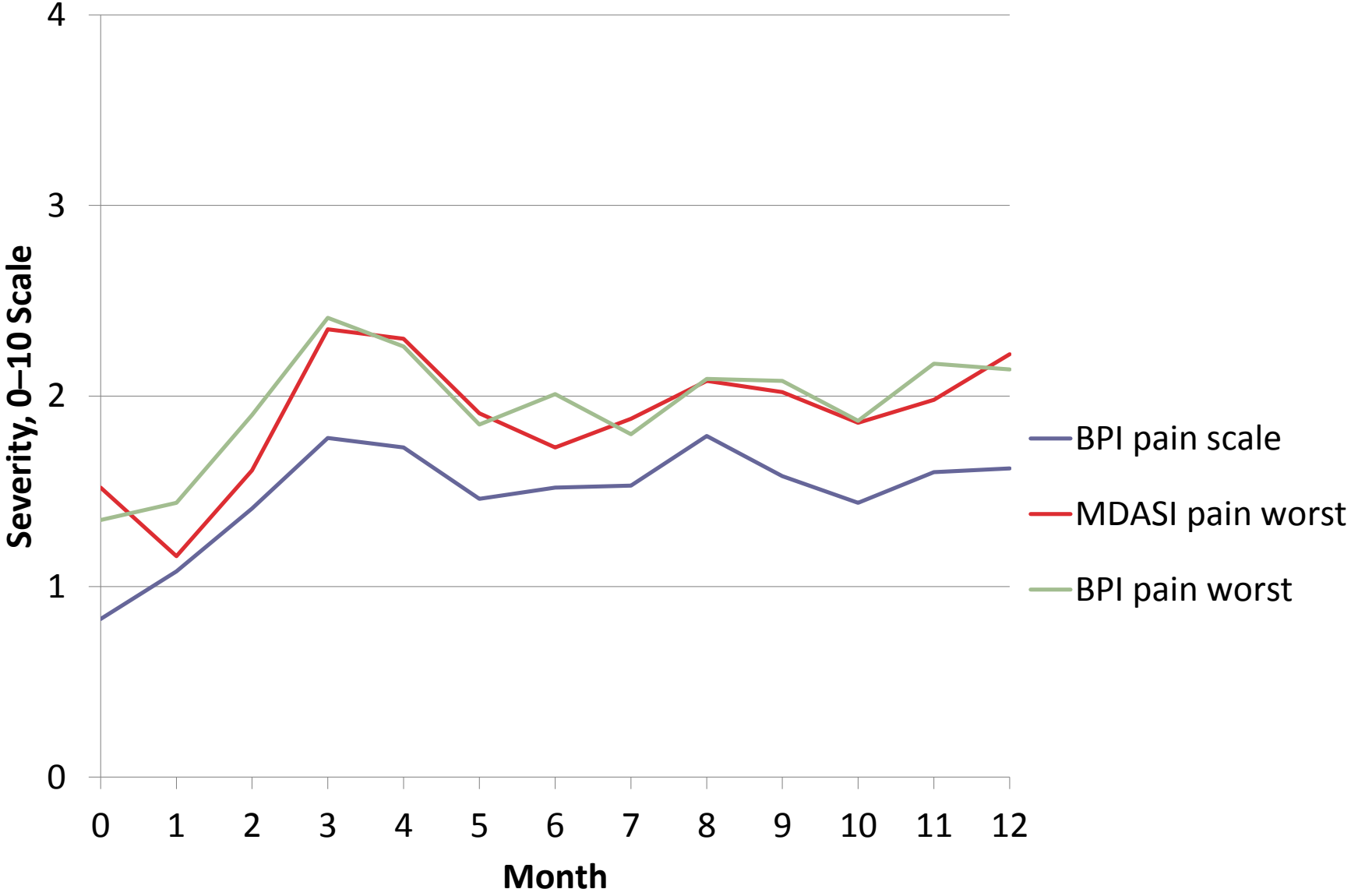
- How might one construct a composite symptom score for patients with lung cancer?

  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, α~.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



Test-Retest Reliability

Correlation coefficients between BPI pain scale and MDASI pain worst					
	Month 0	Month 3	Month 6	Month 9	Month 12
r	0.805	0.789	0.887	0.948	0.950
P	<.0001	<.0001	<.0001	<.0001	<.0001

Intraclass correlation (ICC) of month 3 and 4			
	ICC (95% CI)	**Mean (SD)**	
		Month 3	**Month 4**
BPI pain scale	0.824 (0.689 – 0.903)	1.61 (1.89)	1.73 (1.85)
MDASI pain worst	0.819 (0.681 – 0.901)	2.15 (2.38)	2.30 (2.20)

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

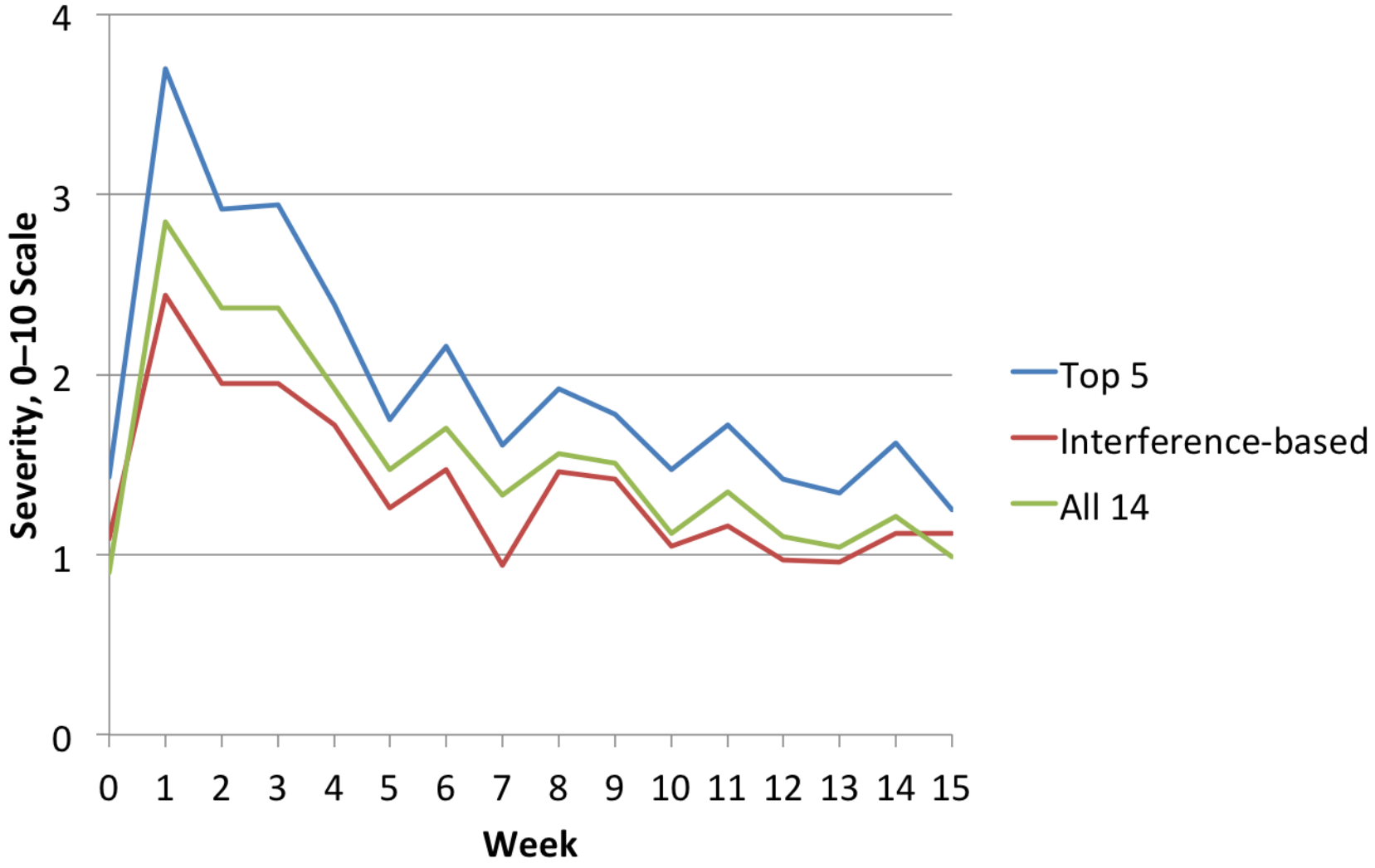
From the MDASI Lung Cancer Module (16 symptoms, Mendoza et al, 2011)

- 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)

Top 5	Interference-Based	All Items
Fatigue	Fatigue	Sadness
Disturbed sleep	Lack of appetite	Distress
Shortness of breath	Pain	Disturbed sleep
Pain	Distress	Drowsiness
Distress	Dry mouth	Fatigue
	Numbness	Difficulty remembering
	Shortness of breath	Dry mouth
	Drowsiness	Lack of appetite
		Numbness
		Vomiting
		Nausea
		Coughing
		Pain
		Shortness of breath

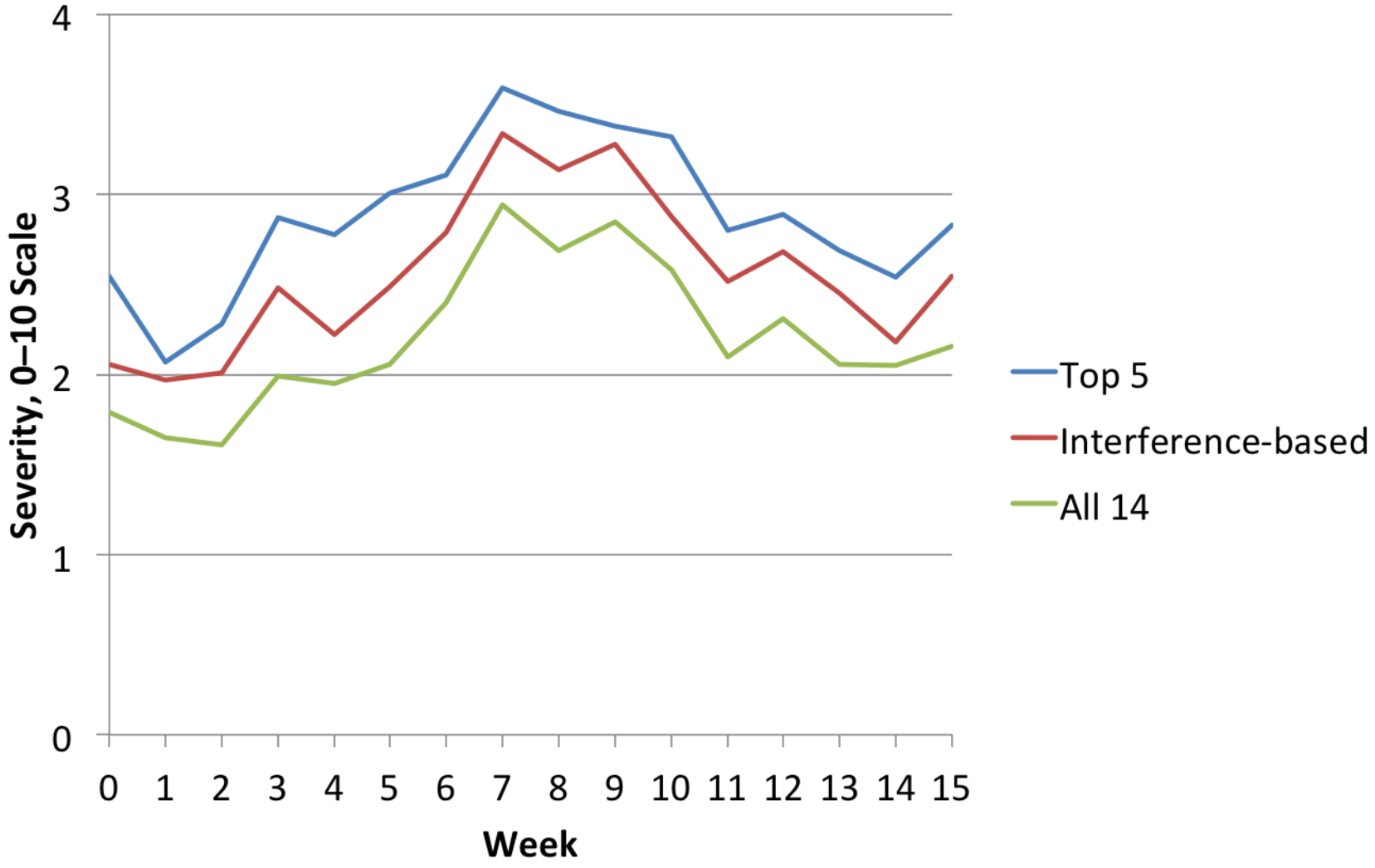
Baseline Symptoms Surgery (N=85)



Baseline Symptoms Chemoradiation (N=52)

Top 5	Interference-Based	All Items
Fatigue	Sadness	Fatigue
Shortness of breath	Coughing	Disturbed sleep
Disturbed sleep	Fatigue	Shortness of breath
Coughing	Drowsiness	Pain
Drowsiness	Nausea	Distress
		Coughing
		Dry mouth
		Lack of appetite
		Drowsiness
		Sadness
		Difficulty remembering
		Numbness
		Nausea
		Vomiting

Baseline Symptoms Chemoradiation (N=52)



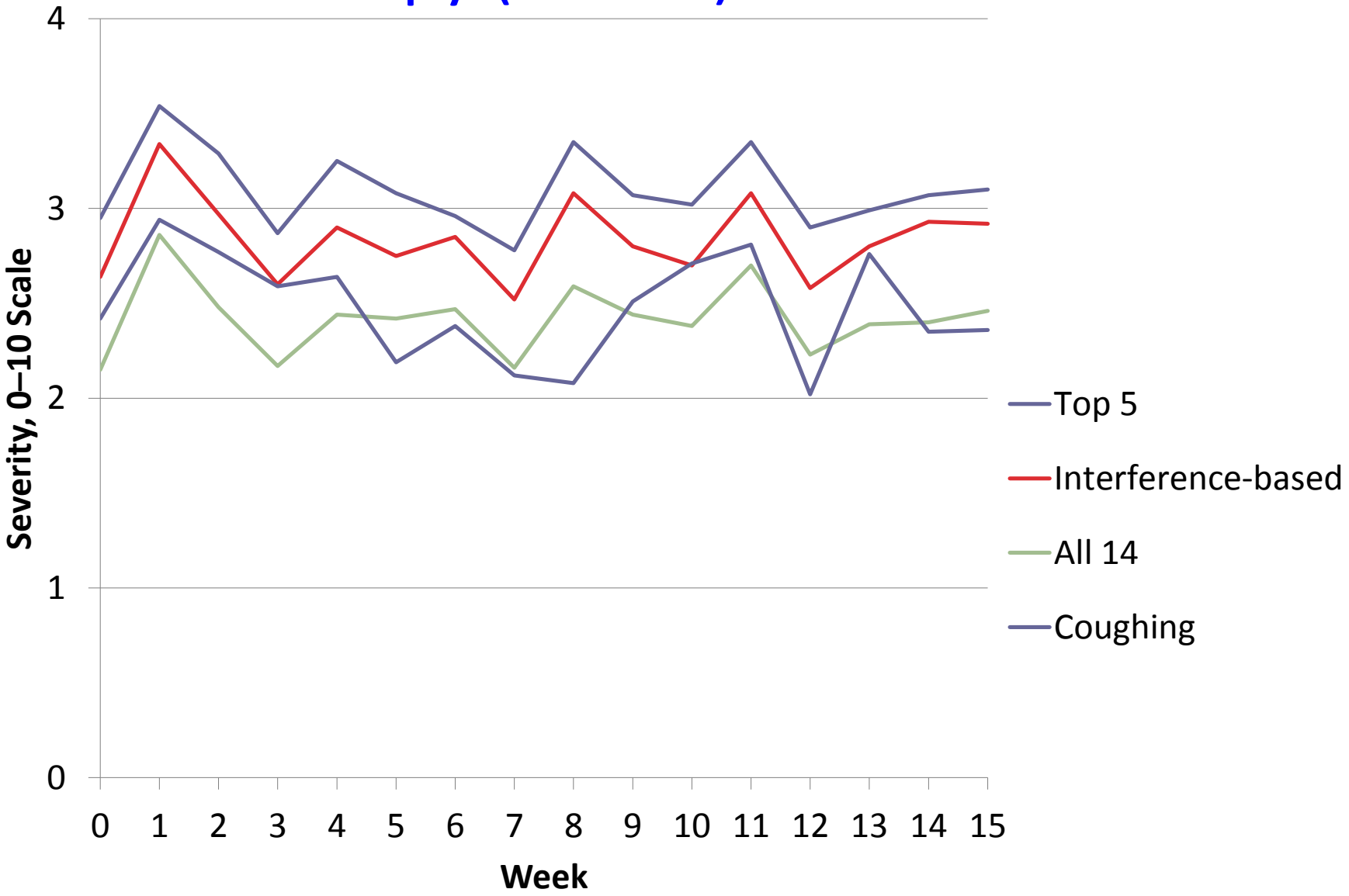
Baseline vs. Peak of Therapy Chemoradiation (N=52)

Baseline	% Moderate to Severe	At Peak (~Day 42)	% Moderate to Severe
Fatigue	36	Fatigue	51
Disturbed sleep	27	Pain	41
Shortness of breath	27	Drowsiness	37
Pain	22	Lack of appetite	27
Distress	20	Disturbed sleep	24
Coughing	20	Distress	24
Dry mouth	16	Nausea	22
Lack of appetite	13	Dry mouth	18
Drowsiness	13	Coughing	18
Sadness	13	Shortness of breath	16
Difficulty remembering	11	Sadness	14
Numbness	4	Vomiting	14
Nausea	0	Difficulty remembering	12
Vomiting	0	Numbness	10

Baseline Symptoms Chemotherapy (N=185)

Top 5	Interference-Based	All Items
Fatigue	Lack of appetite	Fatigue
Shortness of breath	Fatigue	Pain
Disturbed sleep	Dry mouth	Disturbed sleep
Pain	Shortness of breath	Shortness of breath
Drowsiness	Distress	Drowsiness
	Drowsiness	Lack of appetite
		Dry mouth
		Sadness
		Coughing
		Distress
		Numbness
		Difficulty remembering
		Nausea
		Vomiting

Lung Symptoms Chemotherapy (N=185)



Baseline vs. End of Cycle 2 Chemotherapy (N=185)

Baseline	% Moderate to Severe	End of Cycle 2	% Moderate to Severe
Fatigue	35	Fatigue	39
Pain	30	Pain	33
Disturbed sleep	28	Shortness of breath	32
Shortness of breath	27	Distress	30
Drowsiness	24	Disturbed sleep	29
Lack of appetite	23	Numbness	29
Dry mouth	22	Drowsiness	27
Sadness	21	Lack of appetite	26
Coughing	21	Coughing	25
Distress	21	Sadness	23
Numbness	13	Dry mouth	21
Difficulty remembering	12	Difficulty remembering	20
Nausea	7	Nausea	12
Vomiting	3	Vomiting	7

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

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  - Assistant Professor
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  - Doctoral Student, Biostatistics
- Kai-Ping (Eric) Liao, PhD, MHA
  - Senior Data Analyst

Symptom Assessment in FDA Medical Product Labeling

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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)

Symptom bothersomeness ratings ranked by # of times rate		
Symptom (sorted by most to least frequently cited)	# Times cited (out of n=23)	Average bot (1=not at a
Cough (generally)	16	3.7
Fatigue	10	3.6
Chest congestion	9	3.9
Difficulty breathing/ shortness of breath	9	3.8
Wheezing	9	2.7
Headache	6	4.0
Lack of appetite	6	2.2
Coughing up phlegm/sputum	5	3.4
Fever	3	3.0
Tightness in chest	3	4.0
Coughing up blood	3	4.0
Runny nose	3	3.7
Sinus pain	2	4.5
Muscle ache	2	3.0
Urinary incontinence	1	5.0
Pain from cough	1	5.0
Sore throat	1	5.0
Chest pain	1	3.0
Chills	1	3.0
Sneezing	1	3.0
Vomiting	1	2.0
Nausea, stomach ache	1	5.0

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

Goss CH, et al. J Cyst Fibros. 2009 Jul;8(4):2

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

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- 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

EXACT-PRO

Symptomatic Features of COPD Exacerbation

Jones et al. (2011) *Chest* Prepublished online November 11, 2010; DOI 10.1378/chest.10-1240

- 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

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- 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

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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

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Primary Endpoints Used in IBS Clinical Trials for Previously or Currently FDA-Approved Drugs

Product and Specific Indication	Primary Endpoint	Questions Used to Assess Endpoint	Response
Alosetron — IBS-D[1]	Adequate relief	*In the past 7 days, have you had adequate relief of your IBS pain or discomfort?*	Binary endpoint (Yes/No)
Tegaserod — IBS-C[2]	Satisfactory relief	*Over the past week, do you consider that you have had satisfactory relief from your symptoms of IBS?* *Did you have satisfactory relief of your overall IBS symptoms during the last week?* *Did you have satisfactory relief of your abdominal discomfort or pain during the last week?*	Binary endpoint (Yes/No)
	Subject Global Assessment of Relief (SGA)	*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.*	5-Point Likert scale: worse, not at all relieved, somewhat relieved, considerably relieved, completely relieved
Lubiprostone — IBS-C[3]	Modified version of the SGA	*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?*	7-Point Likert scale: substantially worse, moderately worse, slightly worse, no change, slightly improved, moderately improved, substantially improved

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

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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

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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

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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

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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

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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

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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 $\geq$ 30%

- **Stool Consistency Responder**
  - Patient who experiences a $\geq$50% reduction in the number of days per week with at least one stool which has a consistency of $\geq$ type 6 compared with baseline

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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

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  - Director, SEALD, CDER/FDA
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  - 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 : ≥ 4/12 signs and symptoms

Ramsay et al: ≥ 2/7 symptoms + ≥ 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)

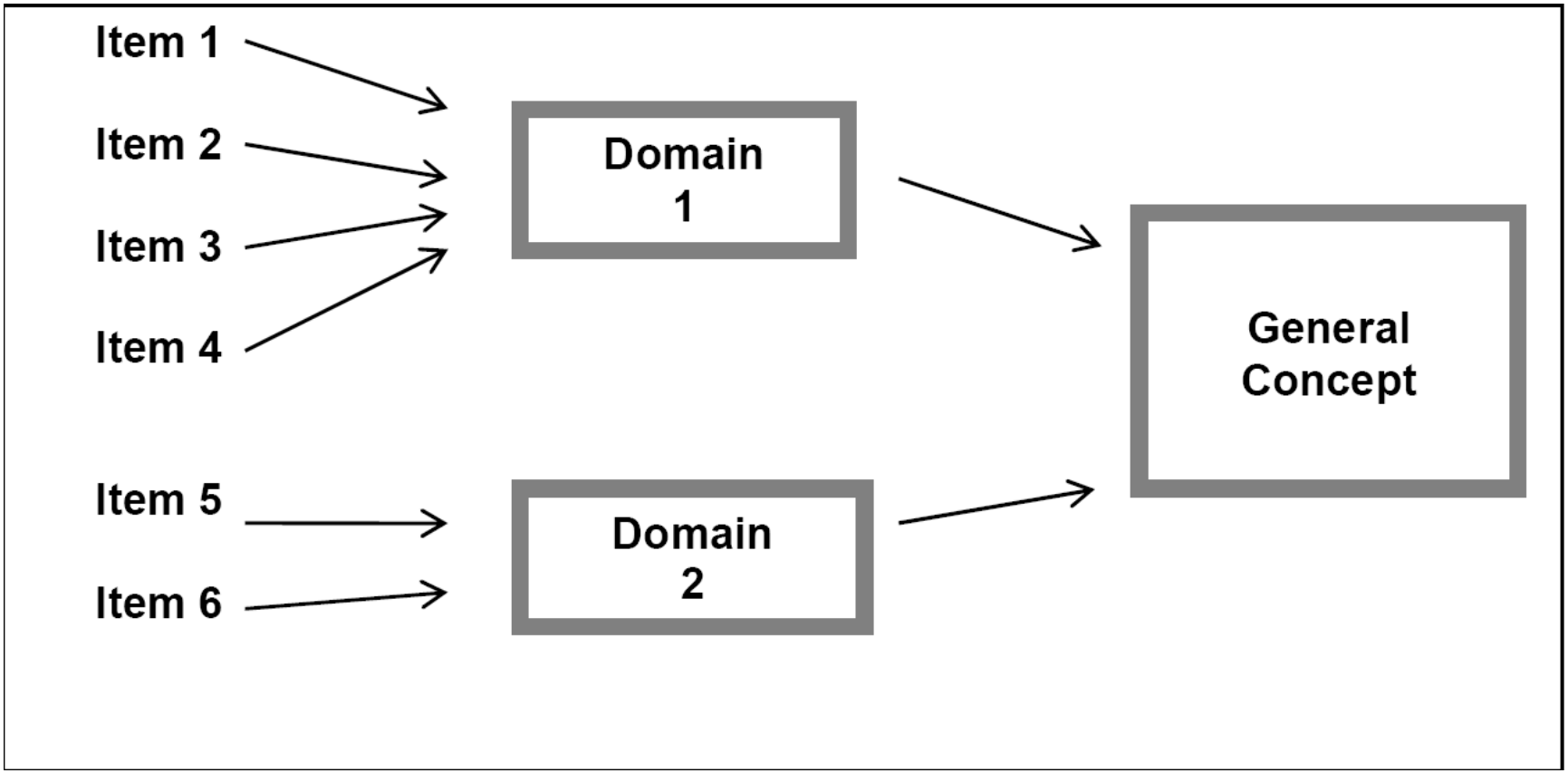
Why track each item?

- 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**.

Multi-items PRO and Multiple Claims (contd)

- 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 → 1 dimension or score (validation of 1 concept)
- Multiple items → 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

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MSWS-12 item, item by item information

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

Fuchs criteria: ≥ 4 out of 12 signs or symptoms

Ramsay et al criteria: ≥ 2 out of 7 symptoms + ≥ 1 out of 3 signs

Source: Quittner and Goss (2007). Patients Reported Outcomes in Cystic Fibrosis. Proc Am Thorac Soc Vol 4. pp 378–386.

Binary multi-items, example 2 Improvement in RA

- Tender and swollen join counts (20% improvement)

AND

- ACR-core set measures: (20% improvement in 3 of the 5 measures)
  - patient global assessment
  - physician global assessment
  - pain
  - disability
  - acutephase reactant

Group of items information, example

Table 3:
Components of ACR Response in Study I

Parameter (median)	Placebo N = 80		ENBREL®[a] N = 78	
	Baseline	3 Months	Baseline	3 Months*
Number of tender joints [b]	34.0	29.5	31.2	10.0[f]
Number of swollen joints [c]	24.0	22.0	23.5	12.6[f]
Physician global assessment [d]	7.0	6.5	7.0	3.0[f]
Patient global assessment [d]	7.0	7.0	7.0	3.0[f]
Pain [d]	6.9	6.6	6.9	2.4[f]
Disability index [e]	1.7	1.8	1.6	1.0[f]
ESR (mm/hr)	31.0	32.0	28.0	15.5[f]
CRP (mg/dL)	2.8	3.9	3.5	0.9[f]

* 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 Questionnaire[1]; 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