

CONCEPTUAL FRAMEWORKS AND GUIDANCE ON STATEMENTS ABOUT PRO FINDINGS IN PRODUCT LABELS AND PROMOTIONAL MATERIALS

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SESSION AGENDA

- Presentation focus
 - Articulating conceptual frameworks and models
 - Content-based labeling statements
- Response from discussant
 - Albert Wu
- General discussion

OVERVIEW OF PRESENTATION

- Strategic planning for successful PRO labels
- Issue of regulatory concern related to PROs
- Conceptual frameworks and models
 - Models linking health outcomes
 - Measurement models
- Content-based labeling statements
 - Content validity
 - Subjective and empirical evidence

PROS AS EVIDENCE OF TREATMENT EFFECTIVENESS

- PRO is measurement of health status that derives directly from patient (with no interpretation by anyone else)
 - Assesses feeling or function
- Why PROs are important?
 - Some treatment effects are known only to the patient
 - Patients provide unique perspective on treatment effectiveness
 - Comprehensive assessment of impact of disease and treatment
- FDA has a narrow focus on effectiveness and safety of treatments
 - Clear and concise statements on effectiveness
 - Comprehensive reporting of safety
 - Worried about false and misleading statements

STRATEGIC PLANNING FOR SUCCESSFUL PRO LABELS

- Think about what you are going to do before you do it
 - Consistent with good science
- FDA advice indicates label claim drives measurement strategy
 - Desired label statements → PRO instruments

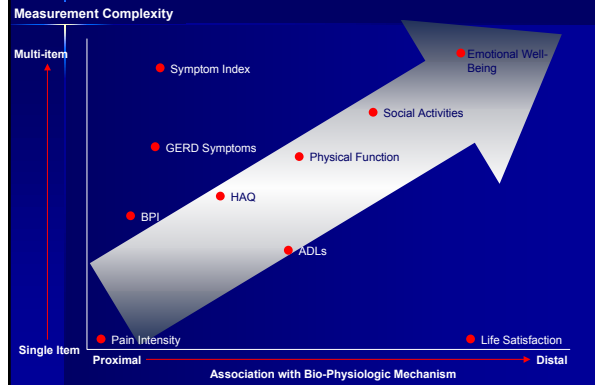
DEVELOPING A SUCCESSFUL PRO MEASUREMENT STRATEGY

- Key steps:
 - Understand disease area and expected treatment effects
 - Identify outcome domains relevant to patient and disease area
 - Articulate endpoint model and conceptual framework
 - Select/develop PRO instruments to measure domains of interest
 - Implement PROs in well-designed clinical trials
 - Communicate early and often with FDA about plans

CONCEPT OF REGULATORY CONCERN RELATED TO PROS

- View PROs as important measures of treatment effectiveness and benefit
- Concerned about clear communication of health outcome benefit
 - Unambiguous statements are key
- Regulatory concern associated with
 - Simple versus complex outcome domains
 - Single-item versus multiple-item measures
 - Overall composite versus single domain scores
 - Distal versus proximal to bio-physiological mechanism

INDEX OF REGULATORY CONCERN AND PRO EVIDENCE



PRESCRIPTION FOR REGULATORY CONCERN (ANXIETY)

- Clear and understandable endpoint model and conceptual framework
- Documented evidence commensurate with measurement complexity
 - Simple, proximal domain → Less evidence
 - Complex, more distal domain → More evidence

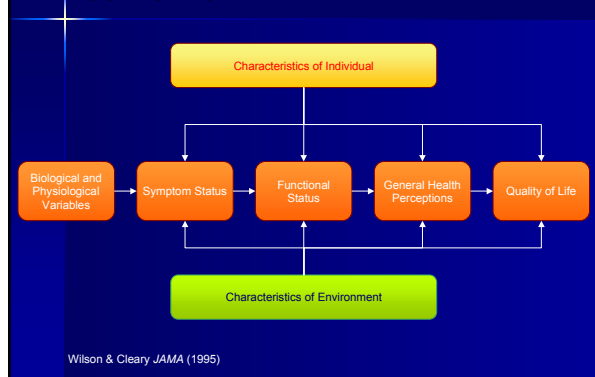
PRO CONCEPTUAL FRAMEWORKS AND MODELS

- Two key components
- Endpoint model
 - Relationship among health outcomes
 - Conceptual framework
 - PRO measurement model

WHAT IS AN ENDPOINT MODEL?

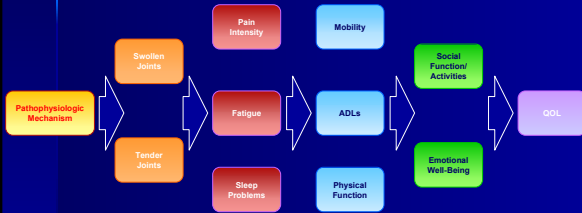
- Endpoint models
 - Articulate associations among different health outcomes
 - Links between clinical and patient-based outcomes
 - Demonstrate importance and association of different health outcomes
 - Not a theoretical framework/model
- Model driven by
 - Patient population
 - Disease characteristics
 - Treatment effects
- Provides rationale for PRO measurement strategy
 - Identifies important PRO domains
 - Explicates association with treatment benefit
 - Proximal versus distal outcomes
- Informs identification of PRO label targets

WILSON-CLEARY MODEL OF HEALTH OUTCOMES



Wilson & Cleary JAMA (1995)

ENDPOINT MODEL EXAMPLE: RHEUMATOID ARTHRITIS AND PROS



EVIDENCE SUPPORTING ENDPOINT MODEL

- Systematic review of disease literature
- Patient and clinician interviews
- Structural equation models (empirical data)

WHAT IS A MEASUREMENT MODEL AND HOW DO YOU KNOW YOU'VE GOT IT?

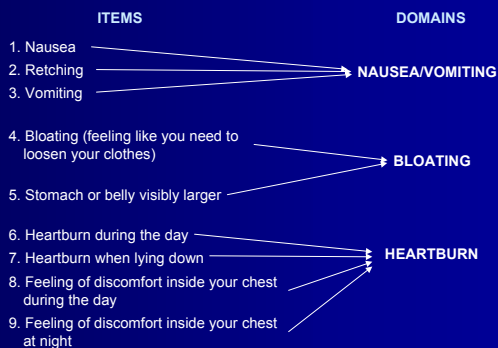
- "Conceptual framework refers to how items are grouped according to subconcepts and domains" (Draft PRO Guidance, 2006)
- PRO measurement model drives instrument content
 - Content map for instrument
 - Shows relationship between items and domains (concepts)
- Sources of information
 - Patient interviews
 - Clinician interviews
 - Medical and health outcome literature

How are PROs Developed? The FDA Perspective

Figure 1: The PRO Instrument Development and Modification Process



MEASUREMENT MODEL FOR AN UPPER GI SYMPTOM SCALE

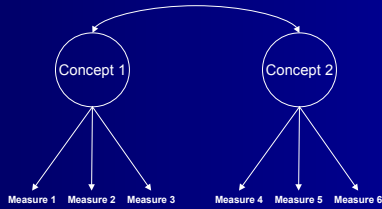


MEASUREMENT MODEL: GUIDE TO INSTRUMENT DEVELOPMENT AND EVALUATION

- Instrument Development
 - Instruments based on sampling of universe of items covering domain (construct)
 - Items represent aspects of domain
 - Guides construction of items to measure the domain (content map)
- Psychometric Evaluation
 - Generates hypotheses about internal structure of PRO instruments
 - Items within domains
 - Domains within aggregate concepts
 - Generates hypotheses for validation
 - relationships among PRO domains
 - relationships between PRO domains and clinical measures

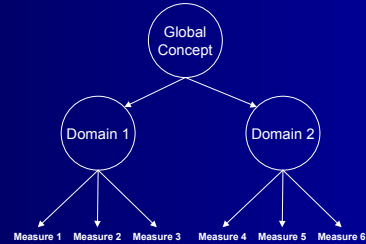
CONCEPTUAL MODEL: INSTRUMENT DEVELOPMENT AND EVALUATION

- To demonstrate a construct exists, one must link the concept with measures
- The concepts are linked and this linkage is evaluated with construct validation



EVALUATE THE INSTRUMENT

- There should be correspondence between the items, the domain score, and the overall score
- *All expectations should be stated prior to the validation process*



EVALUATION OF PRO CONCEPTUAL MODELS

- Qualitative Research Studies
 - Documentation for patient focus group and interview studies
 - Content validity studies
 - Importance and relevance ratings from patient samples
 - Clinician review and importance/relevance ratings
 - Cognitive interviewing and debriefing
 - Needed to identify/confirm conceptual framework
- Issue of face versus content validity

QUANTITATIVE EVALUATION OF PRO CONCEPTUAL MODELS

- Psychometric Evaluation Studies
 - Evidence from exploratory and confirmatory factor analyses
 - Item to domain correlations
 - Items within domain have higher correlations than with other domains
 - Accumulated evidence on construct validity across multiple studies

FACTOR ANALYSIS OF PPMQ-R ITEMS

Item Focus	PPMQ "Satisfaction" Scales			
	Efficacy	Function	Ease of Use	Cost
Relieves migraine pain	0.83			
Relieves other migraine symptoms	0.81			
Speed of pain relief	0.90			
Speed of relief of other migraine symptoms	0.80			
Number of doses needed to relieve pain	0.80			
Consistency of pain relief	0.90			
Consistency of preventing pain from returning	0.69			
Length of pain relief	0.89			
Relief of pain/other symptoms regardless of when medication taken	0.93			
Preventing need for other medications	0.75			
Speed of returning to usual daily activities	0.74			
Productivity in performing usual daily activities		0.80		
Participation in usual social activities		0.88		
Participation in usual family activities		0.92		
Reducing frustration		0.49		
Ease of use			0.78	
Convenience			0.61	
Cost				0.84
Obtaining through insurance				0.68

Source: Revicki et al. (2006)

CONTENT-BASED LABELING AND PROMOTIONAL CLAIMS

- Statement on treatment benefit based on content of PRO instrument
 - Concept (domain) intended to measure
 - Sampling of universe of items
- Challenge is in determining 'content' underlying claim language
- Claim statement based on review and evaluation
 - Subjective versus objective
- Key issues
 - Face validity versus all psychometric evidence
 - Evidence of content validity and meaning

EXAMPLE: HUMIRA LABEL FOR RHEUMATOID ARTHRITIS

- Humira is indicated for reducing the signs and symptoms, including major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active rheumatoid arthritis.
- **Clinical Studies Section**
 - In studies I-IV, HUMIRA showed significantly greater improvement than placebo in the disability index of Health Assessment Questionnaire (HAQ-DI) from baseline to the end of study, and significantly greater improvement than placebo in the health-outcomes as assessed by the Short Form Health Survey (SF 36). Improvement was seen in both the Physical Component Summary (PCS) and the Mental Component Summary (MCS).
 - In Study V, the HAQ-DI and the physical component of the SF-36 showed greater improvement ($P < 0.001$) for the HUMIRA/MTX combination therapy group versus either the MTX monotherapy or the HUMIRA monotherapy group at Week 52, which was maintained through Week 104.

COMMENTS ON HUMIRA LABEL AND PRO ENDPOINTS

- PRO instruments (HAQ, SF-36) are consistent with FDA guidance on evaluation of treatments for rheumatoid arthritis
 - PROs appeared in previous clinical development plans and labels for RA
 - Expected and important patient endpoints
 - ACR response criteria
- PRO information appears both in Indication and Clinical Studies sections of label
- Consistent results observed across several clinical trials
- Label states clearly facts on PRO findings for HAQ and SF-36

DETERMINING CONTENT UNDERLYING CLAIM LANGUAGE

- Claims statements should be based on best description of PRO concept (domain)
 - Content of items
 - Clear and simple language
- Key issues:
 - Simple versus complex (multi-item or multi domain) PROs
 - Multiple item measures add to challenge
 - Consider the evidence
 - Instrument and subscale names may not reflect item content
 - Requires review (essentially subjective opinion)
 - Who decides?

CLAIM STATEMENT BASED ON REVIEW AND EVALUATION

- Subjective versus objective criteria and review
 - Review strength of content validity evidence
 - Requires good documentation
 - Review strength of psychometric evidence (quantitative)
 - Item-subscale analyses
 - Factor analyses
 - Construct validity findings
- Consider all the qualitative and quantitative evidence
 - Face validity should not determine content alone
 - Claim should be a direct and logical derivation of the findings based on the definition of the domains

SUMMARY: WHY DEVELOP AN ENDPOINT MODEL AND CONCEPTUAL FRAMEWORK?

- Represents objective of treatment (FDA 'concepts')
 - Context: population, disease and treatment
 - Describes treatment benefit and subsequent claims
- Clarifies objectives for labeling claims, removes or minimizes ambiguity
- Identifies concepts to be measured
- Guides instrument selection or development to support claims
- Streamlines interaction with the FDA

SUMMARY: EVIDENTIARY REQUIREMENTS FOR ENDPOINT MODEL AND CONCEPTUAL FRAMEWORK

- Clearly describe endpoint model
 - Based on information/evidence from patients, clinicians and literature
 - Empirical studies (structural equation models)
- Clearly summarize conceptual model
 - Rationale for selected PRO domains (concepts)
 - Guidance for selecting existing PRO instrument
 - Content map for new PRO instrument development
- Conceptual framework evidence base – PRO measure
 - Content validity (focus groups and interviewing patients)
 - Exploratory and confirmatory factor analyses
 - Construct validity evidence

DISCUSSION

- Albert Wu