Application of New Patient-reported Outcome Measures and Methods in Psychiatry and Neurology Clinical Trials

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Objectives

- Challenges to application of IRT and CAT-based measures
  - Clinical trial researchers
  - Regulatory agencies
  - Clinicians
  - Study participants
- Advantages of IRT and CAT-based measures for CNS clinical trials

Introduction

- IRT-based methods and CAT provide innovative solutions to the challenges of assessing health status in subjects with varying problems and trajectories of change over time
- Uncertainty whether clinical researchers, health products industry and regulatory agencies will fully accept IRT-based measurement
- For CNS clinical trials, some study participants may have difficulty in responding to CAT measures (no different than other modes of administration)
- Challenges with placing new CAT-based measures and existing static measures on same metric (do we lose past history?)

Challenges for Clinical Trial Researchers

- Significant barriers may be:
  - Lack of understanding and familiarity with IRT-based methods
  - Skepticism about patient-reported outcomes for some study participants (i.e., schizophrenia, mania, etc.)
  - Practical issues and feasibility
- IRT-based and CAT requires computer availability and administration
  - May not be practical in many research settings
  - Potential increase in research-related costs
- Sufficient trade-off in increased responsiveness and ability to detect clinically meaningful changes

Adaptation Needed for Different Health Assessments

		Main Study		
Degree of Adaptation	Pilot	Time 0	Time 1	Time 2
None	General Short Form	General Short Form	General Short Form	General Short Form
Moderate	General Short Form	Custom Short Form	Custom Short Form	Custom Short Form
High	CAT	Custom Short Form	Custom Short Form	Custom Short Form
Extreme	CAT	CAT	CAT	CAT

Challenges for Regulatory Agencies

- Regulatory agencies have limited experience with IRT and CAT methods
- Focus on static, disease-specific health outcome measures and documentation on instrument development, content validity, psychometric qualities, and responsiveness and interpretation
- Challenge of demonstrating content/face validity of subsets of questions in a large item bank
- Can acceptable short, disease-specific measures be developed from large generic domain item banks?
- Cognitive discontinuity associated with IRT-based and tailored health outcome measures

Challenges for Health Products Industry

- Adaptation driven to some extent by regulatory agency (FDA, EMEA) guidance and perspective
- Few sponsors will select IRT-based measures if they are not acceptable to regulatory agencies
- IRT-based and CAT may prove acceptable to the FDA if documented evidence supporting content validity, good psychometric qualities, and guidance on interpretation of results
- Key issue is trade-off between potential expense and probability of demonstrating effectiveness of new treatments

Challenges for Clinicians

- Need practical, easily applied, and understandable measures
- Clinicians may not care about precise assessment of single domains, but need tools to assist in diagnosis and evaluation
  - For example, in pain assessment after determining pain intensity, next questions may need to focus on:
    - Mobility
    - Activity limitations, and
    - Function to evaluate treatment
- Can IRT-based measures be developed with logical branching networks to assist clinicians in efficiently evaluating patient status for treatment decision-making?

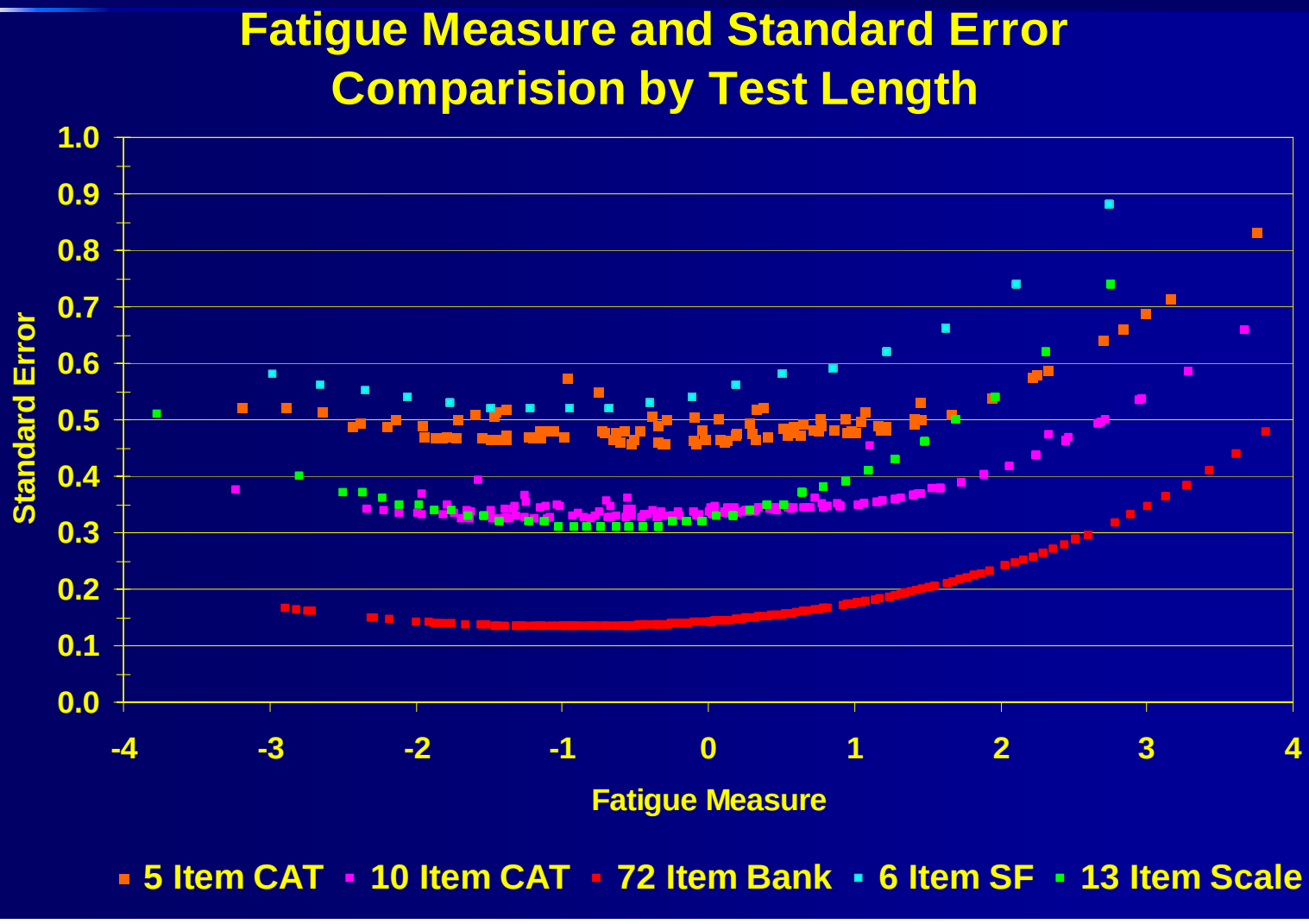
Challenges for Study Participants

- Study participant acceptance is critical for application of CAT measures
- Potential advantages of brief, psychometrically sound outcome assessments (less respondent burden)
- Few problems completing computer administered instruments and ePROs
  - Challenges for some subjects (elderly, low education, poor physical health)
- Further research needed in severe psychiatric disorders, but same challenges as self-completed health outcome measures

Advantages Of IRT and CAT-Based Measures for CNS Clinical Trials

- Allows for improved domain coverage (minimal floor and ceiling effects)
- Improved measurement precision for short-forms and CAT instruments
- Flexibility for longitudinal research (including clinical trials)
- Preliminary evidence of responsiveness of IRT-based short-form instruments

Fatigue Measure and Standard Error Comparison by Test Length



Varying Length Measures in Longitudinal Studies

- STANDARD
  - Scores on brief and long measures are on different metrics
  - Cannot be combined for more powerful longitudinal statistical models
- IRT/CAT
  - Scores on brief and long measures are on same metric
  - Maximum, efficient use of data collected over time

Treatment Comparisons and Effect Size Estimates for Baseline to Endpoint Changes for Depression Severity Scales for Paroxetine and Placebo Groups

Study	Score Change	Least Square Mean Change		F-Value	P-Value	Effect Size
		Paroxetine	Placebo			
A1651008b	HDRS Total	-11.44	-8.38	7.45	0.007	0.43
	MADRS Total	-13.62	-8.79	11.93	0.001	0.54
	DS-1 T-Score	-17.33	-12.17	8.73	0.004	0.46
	DS-2 T-Score	-21.92	-13.69	14.57	0.0002	0.59
	DS-3 T-Score	-23.14	-14.23	16.09	0.0001	0.63

Sample size: Paroxetine N = 82; Placebo N = 85

Advantages of Short-forms Developed from PROMIS Item Banks

- Select a set of items that are matched to the severity level of the target population
- All scales assembled from the same item bank are linked on the same metric

Advantages of CAT-based Assessment

1. Provide an accurate estimate of a person's score with the minimal number of questions
   - Questions are selected to match the health status of the respondent.
2. CAT minimizes floor and ceiling effects
   - People near the top or bottom of a scale will receive items that are designed to best assess their health status.

Interim Solution for Sponsors, Clinical Researchers, and Regulatory Agencies

- Continued dialogue among clinical researchers, psychometricians, industry researchers and regulatory agencies
  - Methods for incorporating IRT-based CAT into clinical trials
  - Documentation of psychometric characteristics
  - Experience in interpreting findings
- Initially start with ‘static’ health assessments based on IRT methods and tailored to specific disease indication (interim stage)
- Accumulate experience and evaluate feasibility and responsiveness of CAT in clinical trials as secondary or exploratory endpoints

Summary and Conclusions

- IRT-based short forms and CAT measures have potential to improve efficiency for assessing patient-reported health outcomes
- Availability of PROMIS developed item banks for emotional distress, physical functioning, pain, fatigue and social functioning allow for flexibility for construction of tailored short-form measures
- Continued educational efforts are needed to help clinicians, clinical researchers, regulatory agencies, and health products industry understand IRT methods and applications
- Further research is needed to examine the advantages and disadvantages of IRT-based short-from and CAT measures in CNS clinical trials