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**RARE DISEASE WORKSHOP SERIES**  
Improving the Clinical Development Process

# Interpretation of Health Outcomes Data Within Rare Disease Clinical Trials

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# Objectives

1. Understand methodologies for estimating responder definitions
2. Walk through an example in a rare disease
3. Understand use of cumulative response distribution curves and their value



# Interpretation

- Not considered a measurement property
- Interpretation of health outcome endpoints, including PROs, follow similar considerations as for all other endpoint types used to evaluate treatment benefit of a medical product



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# Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

*Additional copies are available from:*

*Office of Communications, Division of Drug Information  
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Food and Drug Administration  
10903 New Hampshire Ave., Bldg. 51, rm 2201  
Silver Spring, MD 20993-0002*

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*Office of Communication, Outreach, and Development, HFM-40  
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Center for Drug Evaluation and Research (CDER)  
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**December 2009  
Clinical/Medical**





# Interpretation is More Than Achieving Statistical Significance

- Need to achieve statistically significant differences between the active treatment and placebo arms for clinical trials, but it's just not enough (but *is* the way to properly power most trials with a continuous endpoint measure!)
- Need a way to interpret if statistically significant differences are meaningful and important to clinical trial participants
- Can't rely on the statistical significance to demonstrate an interpretable difference
  - Many PRO scales and other health outcomes are new to label readers and familiarity with what types of changes are important requires experience over time



# How Do You Determine the *Responder* *Definition?*



# Key to Interpretation: Responder Definition

- Defined as the trial-specific important difference standard or threshold applied at the individual level of analysis
- This represents the individual patient PRO score change over a predetermined time period that should be interpreted as a treatment benefit



# Responder Definition

- The responder definition is determined empirically and may vary by target population or other clinical trial design characteristics
- FDA reviewers will evaluate a PRO instrument's responder definition in the context of each specific clinical trial



# Anchor-Based Methods

- Anchor-based methods explore the association between the targeted concept of the PRO instrument and the concept measured by the anchors
- To be useful, the anchors chosen should be easier to interpret than the PRO measure itself



# Anchor-Based Methods

- The related response between targeted PRO instrument and the closely-related concept can provide meaning or interpretation of change in a PRO measure
- Anchor selection should have intuitive meaning





# Example Types of Anchors

- Clinical measure
  - *a 50% reduction in incontinence episodes* might be proposed as the anchor for defining a responder
- Patient global ratings



# Patient Global Ratings

- Useful in defining a responder definition *a priori*
- Not intended as labeling claims
- Two Types:
  - Patient global rating of change 
  - Patient global rating of concept 



# Patient Global Rating of Change



- Comprehensive evaluation of complex concept
- Comparative
- Usually a long recall period
- Less desirable due to long recall period



# Patient Global Rating of Concept



- Comprehensive evaluation of complex concept
- Non-comparative (e.g., rating of current condition)
- Minimal or no requirement for patients to average their condition over long periods of time
- Example: “How would you rate your IBS symptoms overall over the past seven days?”
  - Question used at **baseline** and at **endpoint** (cross-sectional)



# Rare Disease Example of Responder Definition

Qual Life Res

DOI 10.1007/s11136-009-9509-8

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**Psychometric validation of two patient-reported outcome measures to assess symptom severity and changes in symptoms in hereditary angioedema**

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# HAE

- Hereditary angioedema (HAE) is a rare autosomal dominant disorder affecting approximately 1 in 10,000 to 50,000 persons worldwide
- Symptoms of HAE are characterized by recurrent, highly variable, acute episodes (attacks) of swelling of any part of the body, including the face, larynx, gastrointestinal tract, extremities, trunk, and/or genitals.



## 2 New HAE PROs Developed for Clinical Trials

- Treatment Outcome Score (TOS)
- Mean Symptom Complex Severity (MSCS)
- Secondary analysis of DX-88/14 EDEMA3<sup>®</sup> clinical trial data pooled across treatment and placebo groups
- N = 71 with baseline and 4 hour responses



# MSCS

- MSCS score is a point-in-time measure of symptom severity.
- At baseline, 4 and 24 hours, patients rated the severity on a categorical scale (0 = normal, 1 = mild, 2 = moderate, 3 = severe) for symptoms at each of 5 affected anatomical location.
- Ratings were averaged to obtain the MSCS score; a decrease in MSCS score reflects an improvement in symptoms.



# TOS

- TOS is a measure of symptom response to treatment.
- At 4 and 24 hours, patients assess response characterized by their change from baseline in symptom severity on a categorical scale:
  - significant improvement = 100
  - improvement = 50
  - same = 0
  - worsening = -50
  - significant worsening = -100



# Patient Global Item

- The Global Improvement Measure is a single-item categorical response assessment of overall improvement in symptoms filled out by patients at 4 and 24 hours.
- Response assessment categories are all relative to baseline.
- The categories were: significant improvement, improvement, same, worsening, and significant worsening.



# Anchor-Based Results at 4 Hours

	Significant Improvement ( <i>N</i> = 30)	Improvement ( <i>N</i> = 21)	Same ( <i>N</i> = 18)	Worsening ( <i>N</i> = 1)	Significant worsening ( <i>N</i> = 1)
TOS at 4 h	93.7 (3.5)	44.7 (4.2)	3.6 (4.5)	-35.9	-97.2
MSCS at 4 h	-1.4 (0.1)	-0.9 (0.1)	-0.3 (0.1)	-0.8	0.3



# Support from Distribution-Based Results

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	1/2 SD	SEM*
TOS (4-h)	23.13	31.58
MSCS (baseline)	0.25	0.31

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The SEM is calculated by multiplying the SD by the square root of  $(1 - ICC)$



# Missing from the PRO Guidance

## Minimum Important Difference (MID)!



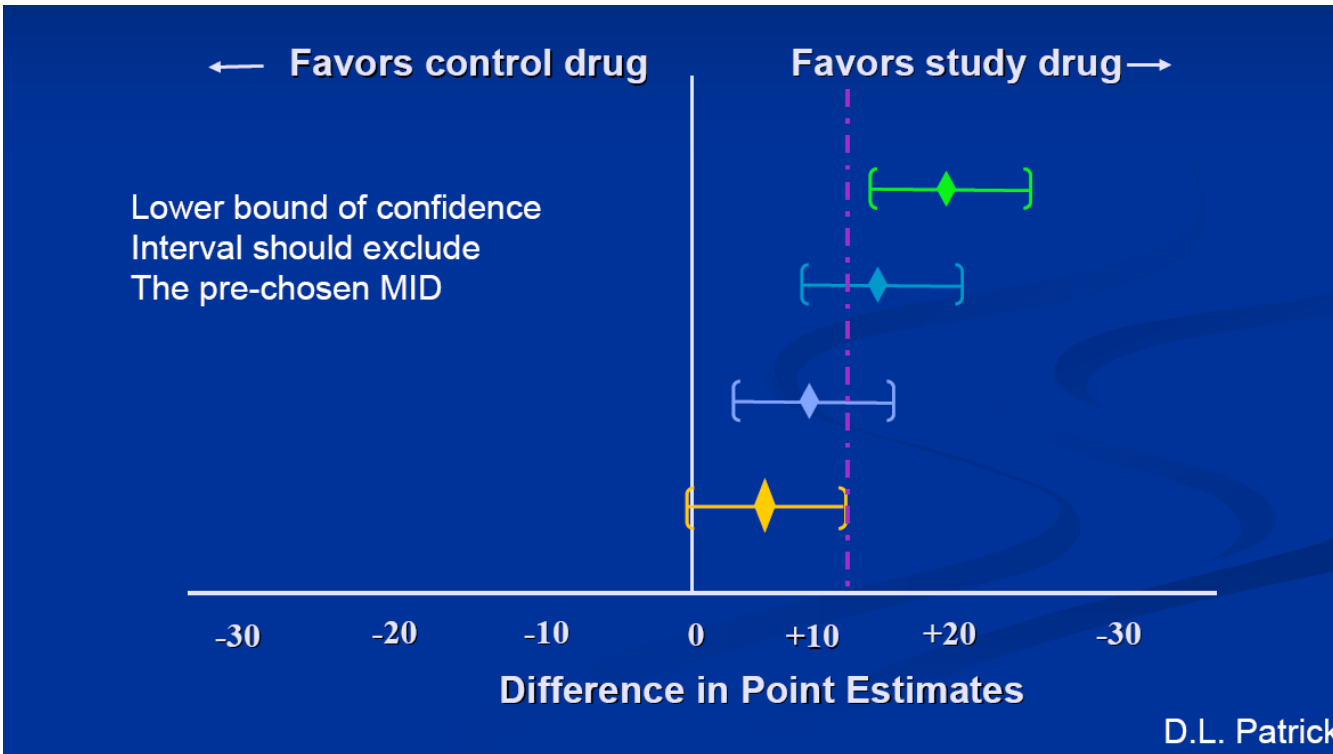
# Minimum Important Difference (MID)

- Defined in *Draft* PRO Guidance (2006) as:
  - The smallest difference between clinical trial treatment arm mean change from baseline (point estimates) that will be interpreted as important
- MID represents the between groups criterion that needs to be met or exceeded in order for study results to be considered clinically meaningful



# Ruling Out an Important Difference

To demonstrate that the treatment difference is statistically significantly larger than the MID, the lower bound of the confidence interval for the treatment difference should exceed the chosen MID





# MID

- Why is MID not included in Final PRO Guidance?
  - Term is interpreted inconsistently (intra-patient change vs. inter-group difference of mean change from baseline)
  - Point estimates of the difference in means between two groups may mask important changes for individual patients or types of patients in each group
  - Responder definitions offer a direct approach to intra-patient change and treatment differences across a range of clinical anchors that can be presented in a cumulative distribution function



# Cumulative Distribution Function



# Cumulative Distribution Function

- An alternative or supplement to responder analysis
- Mentioned prominently in the 2009 FDA Guidance on PRO label and promotional claims

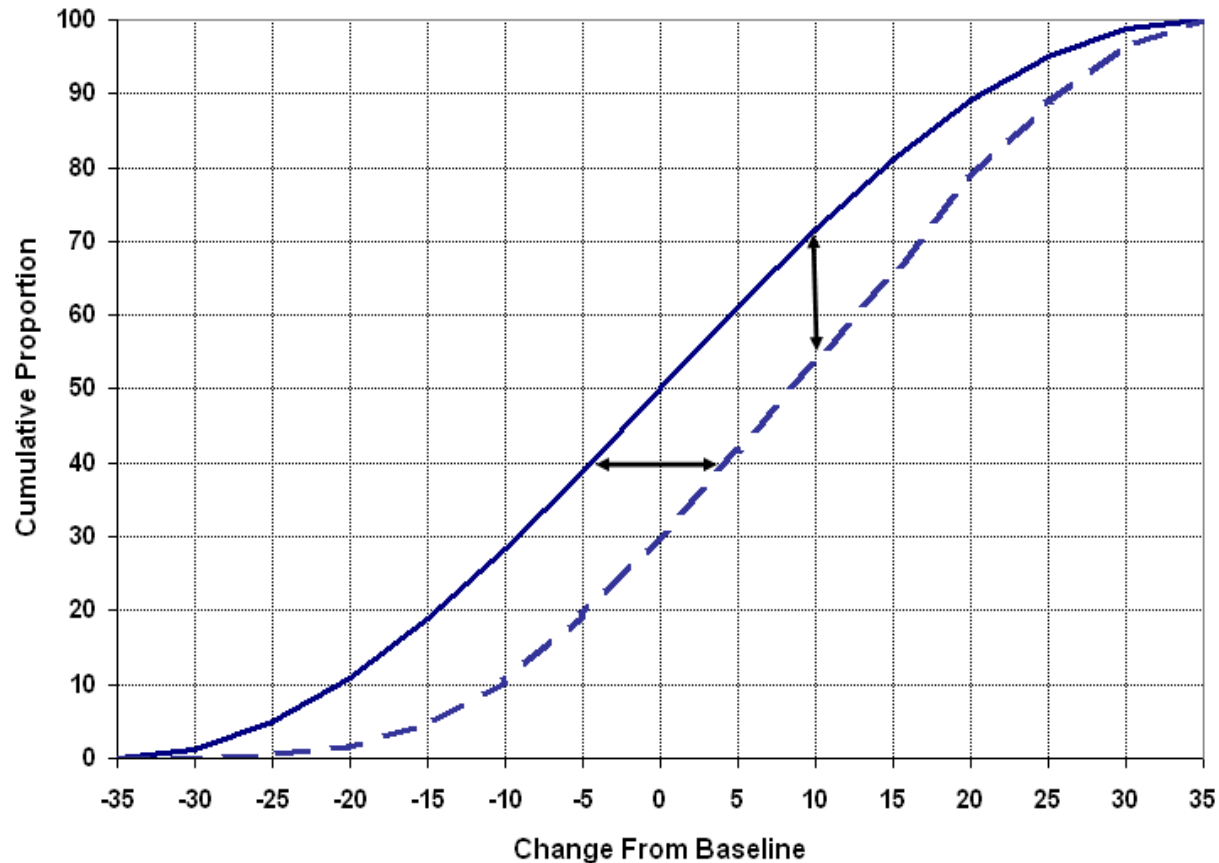


# Cumulative Distribution Function

- Display a continuous plot of the percent change (or numeric change) from baseline on the horizontal axis and the cumulative percent of patients experiencing up to that change on the vertical axis
- Such a cumulative distribution of response curve – one for each treatment group – would allow a variety of response thresholds to be examined simultaneously and collectively, encompassing all available data



## Illustrative Cumulative Distribution Function: Experimental Treatment (solid line) better than Control Treatment (dash line) -- Negative changes indicate improvement





# Aricept® Label from 10/13/2006

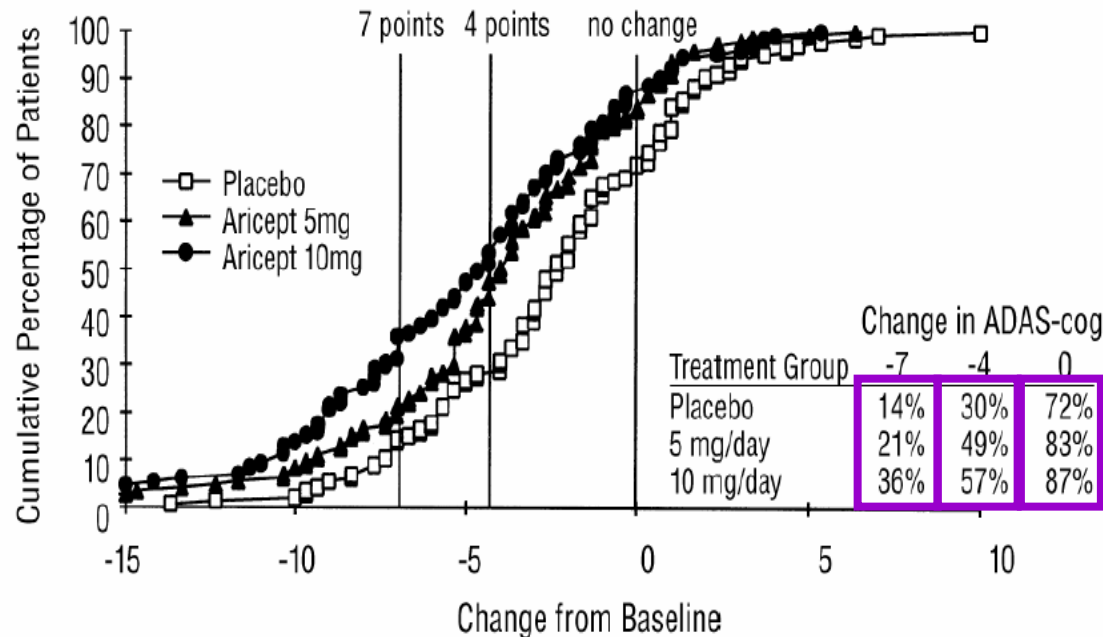


Figure 5. Cumulative Percentage of Patients with Specified Changes from Baseline ADAS-cog Scores. The Percentages of Randomized Patients Within Each Treatment Group Who Completed the Study Were: Placebo 93%, 5 mg/day 90% and 10 mg/day 82%.



# Cymbalta® Label from 11/19/2009 (x-axis reversed)

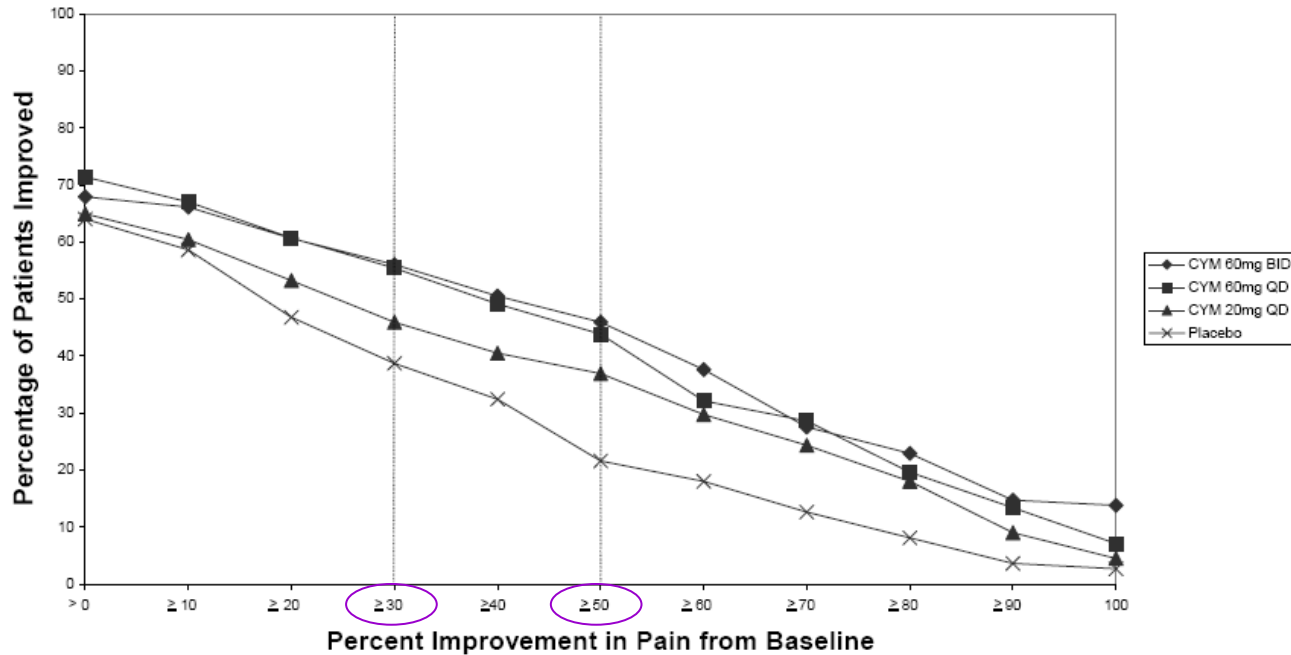


Figure 1: Percentage of Patients Achieving Various Levels of Pain Relief as Measured by 24-Hour Average Pain Severity - Study 1



# Questions?

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