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Patient-reported Outcome Instruments: Overview and Comments on the FDA Draft Guidance

June 19, 2006



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Learning Objectives

- 1. Summarize FDA draft guidance regarding patient reported outcome measures.
- 2. Discuss current comments concerning the draft guidance.



Published 2 Feb 2006 in draft as a level 1 guidance according to FDA's Good Guidance Practices

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

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.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be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance.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 Laurie Burke (CDER) 301-796-0700, Toni Stifano (CBER) 301-827-6190, or Sahar Dawisha (CDRH) 301-594-3090.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)

February 2006
Clinical/Medical

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1/19/2006



Represents FDA's current thinking on the use of PRO measures to support labeling claims for medical products regulated by CDER, CBER, and CDRH

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.



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Why use PRO measures?

- Some treatment effects known only to the patient
- Formal assessment more reliable than informal interview
- Patient perspective augments other measures



What is a patient-reported outcome?

PRO

- Element of feeling or function affected by disease
 - Reported directly by patients

PRO instrument/measure

- A tool for measuring function or feeling
 - Reported by patients in a clinical trial

PRO Concept

- Notion of treatment benefit that is the goal of measurement.
 - May be simple or complex.
 - “PRO” ≠ a concept.
 - “QOL”: weak concept for medical product development
 - “HRQL”: multi-domain concept representing patient’s overall perception of the impact of a condition and its treatment



FDA Solicits Comments

- Submit comments at:
 - <http://www.fda.gov/ohrms/dockets/>
- See submitted comments at:
 - <http://www.fda.gov/ohrms/dockets/dockets/06d0044/06d0044.htm>
- Comment period officially closed April 4 but comments will be accepted at any time
- Include docket number with your comments:
Docket No. 2006D-0044



50+ sets of comments received

Academia/Research (10)

Association (9)

Drug Industry (15)

Device Industry (1)

Consulting Industry (14)

Individual Consumer (1)

FDA will consider all comments when writing final guidance

Final guidance will be published “soon”



Expected guidance revision based on comments received

- Instrument conceptual framework
- Study design and labeling implications
- Statistical analysis and interpretation
 - Multiplicity
 - Missing data
 - Interpretation





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Conceptual Framework of an Instrument

June 19, 2006

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Conceptual Framework - Outline

- Treatment Benefit vs. Product Claims
- Endpoint Model → Conceptual Framework
- Anticancer Products as Examples



What is Treatment Benefit?

- Direct Measures of Improvement
 - Survival
 - How patient feels, or
 - How patient functions
- Surrogate Measures of Improvement
 - Examples: blood pressure, cholesterol, HbA1c
- PROs are Direct Measures of Improvement



What is a Claim?

- Statement or implication of treatment benefit
- Require substantial evidence by regulation
- PROs may relate to safety or efficacy claims



What is an Endpoint Model?

- A set of relationships among measures
- Defined by
 - Population
 - Disease
 - Treatment
- Key driver of protocol design



Example: Primary Brain Tumors

- January 2006 AACR/FDA/NCI Public Workshop: Clinical Trial Endpoints in Primary Brain Tumors

Nature of Benefit

Absence of tumor

Physical Function

Neurologic Function

Cognitive Function

Potential Confounders

Measured Concepts / Domains

MRI Imaging

PRO: activities of daily living

Standardized neurologic exam

- Learning/memory
- Speech
- Executive functions

Steroid Use



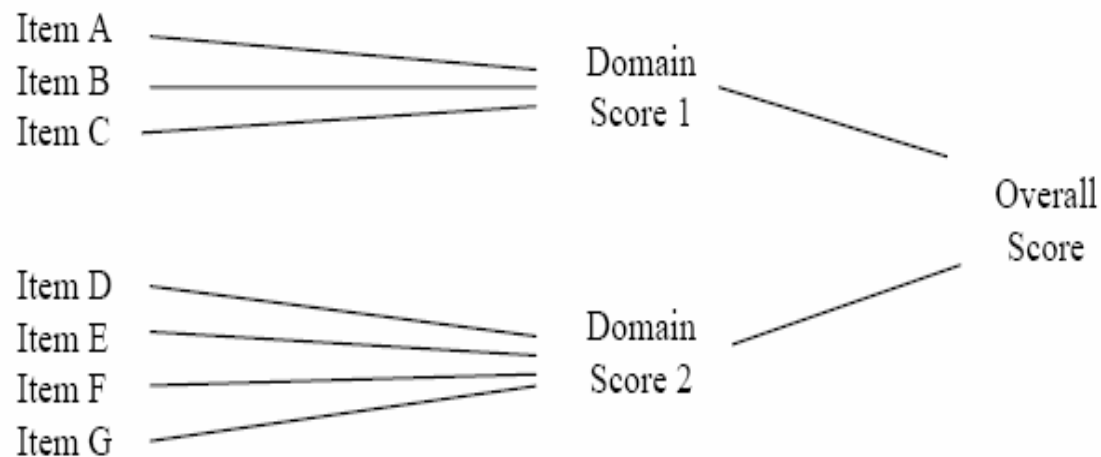
Endpoint Model → Conceptual Framework

- Endpoint model
 - Identifies appropriate endpoint concepts
 - Relates such concepts to one another
 - Points to appropriate trial designs to support claims
- Conceptual framework
 - Defines each endpoint measure
 - Maps items of measurement to domains of interest
 - May evolve in an iterative process of validation



What is a Conceptual Framework?

Figure 2: Diagram of a Conceptual Framework



- Description of how each item relates to the intended measurement concepts



Why develop an Endpoint Model and Conceptual Framework?

- Represents goals of treatment (“concepts”)
 - Context: Population, Disease, Treatment
 - Describes Treatment Benefit and Consequent Claim(s)
- Clarifies goals for labeling claim(s)
- Identifies concepts to be measured
- Guides instrument development to support claims
- Streamlines interaction with FDA



Cancer Approval Endpoints

Historical Order	When Introduced	Effect Measured	Benefit Measured	Need for Blinding
Tumor Shrinkage	1950s	Drug	Surrogate	No
Overall Survival	1980s	Drug plus natural history	Direct	No
Symptom Palliation	1980s	Drug in disease setting	Direct	Yes
Time to Event (PFS, TTP)	1990s	Drug plus natural history	Surrogate	Yes



PROs in Cancer Approvals: '95-'04

Product	Year	Domains	N
Photofrin	1995	Dysphagia	1
Gemzar	1996	Pain/PS/Weight	2
Novantrone	1996	Pain	1
Topotecan	1998	Symptoms (9)	1
Amifostine	1999	Xerostomia	1
Palifermin	2004	Mucositis	1

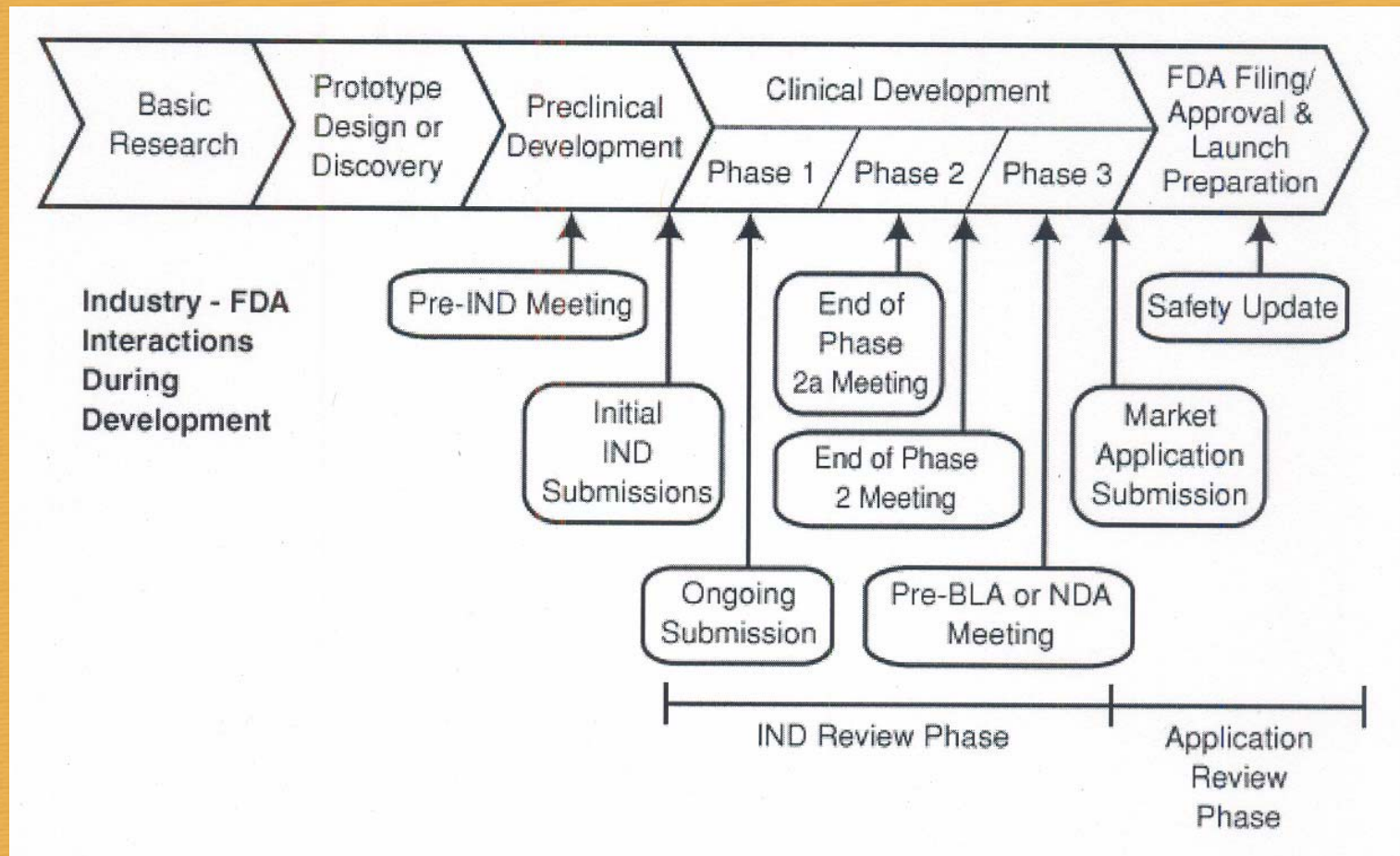


PROs in Cancer Approvals

- Guidance recapitulates practice
 - Endpoint model → Conceptual Framework
- Simple instruments prevail
- Planning is imperative



Critical Path opportunities to discuss measurement issues





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Regulations and Study Design

June 19, 2006

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Indications

- Indications based upon recognized disease or condition
- Disease (as defined in the dictionary) is an abnormal physiological state manifested by signs and symptoms in the patient
- In many diseases a constellation of signs and symptoms (rather than a single manifestation) define the disease under study
- “Claims” include indications but can include anything else included in labeling e.g. clinical studies section



Indications

- 21CFR201.57(c)(1)(i)
 - *“The drug is indicated in the treatment, prevention, or diagnosis of a recognized disease or condition, e.g., penicillin is indicated for the treatment of pneumonia due to susceptible pneumococci; and/or”*
- 21CFR201.57(c)(1)(ii)
 - *“The drug is indicated in the treatment prevention, or diagnosis of an important manifestation of a disease or condition, e.g. chlorothiazide is indicated for the treatment of edema in patients with congestive heart failure; and/or”*



Indications

- 21CFR201.80(c)(1)(iii)
 - *“The drug is indicated for the relief of symptoms associated with a disease or syndrome, e.g. chlorpheniramine is indicated for the symptomatic relief of nasal congestion in patients with vasomotor rhinitis; and/or”*
- 21CFR201.80(c)(1)(iv)
 - *“The drug, if used for a particular indication only in conjunction with a primary mode of therapy, e.g. diet, surgery, or some other drug, is an adjunct to the mode of therapy.”*



Adequate and Well-Controlled

- 21CFR201.80(c)(2)
 - ***“All indications shall be supported by substantial evidence of effectiveness based on **adequate and well-controlled studies** as defined in § 314.126(b) of this chapter”***



Adequate and Well-Controlled

1. Clear statement of objectives
2. Study design permits valid comparison (appropriate control)
3. Select patients with disease (treatment) or at risk of disease (prevention)
4. Baseline comparability (randomization)
5. Minimize bias (blinding, etc.)
6. Appropriate methods of assessment of outcome
7. Appropriate methods of analysis

» 21 CFR 314.126



Adequate and Well-Controlled

- 21CFR314.126(b)(6)
 - *“ The methods of assessment of subjects’ response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and the criteria used to assess response.”*



Why Do Effective Drugs Fail?

- **Random error** = due to sample not representative of population as a whole
- **Bias** = systematic error that results in deviation of results from “true” results
- **Confounding** = error where the measured result is the actual measure but not due to treatment received

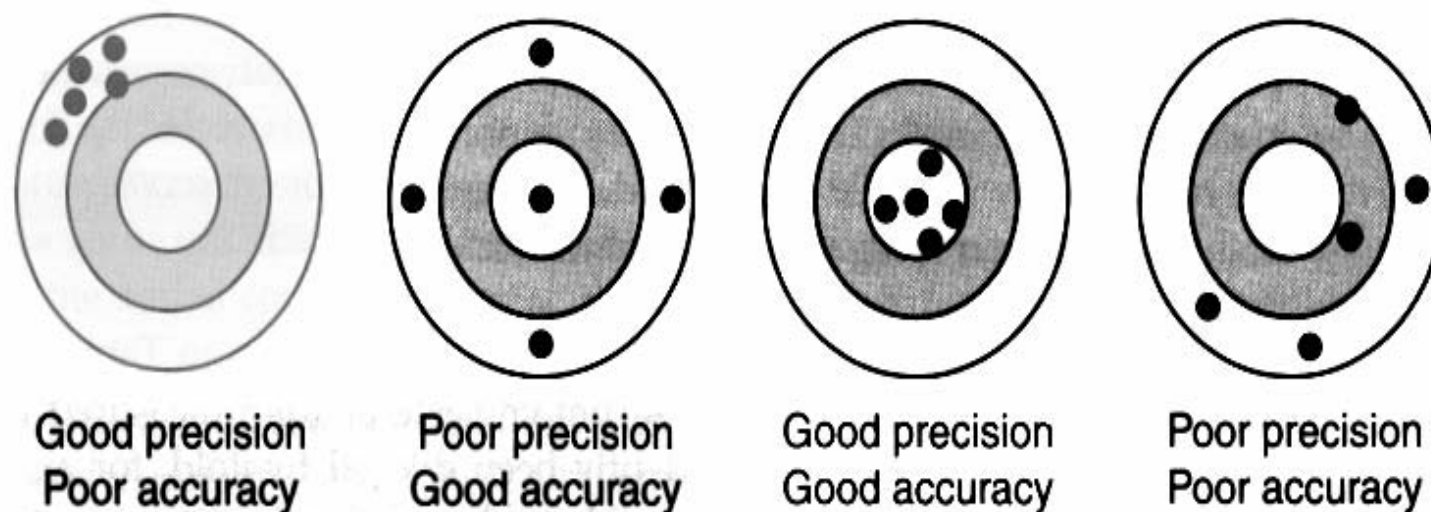


Why Do Effective Drugs Fail?

- Bias and confounding addressed by study appropriate trial design
- Random error addressed by
 - Increasing sample size
 - Not efficient
 - Does not correct for bias and confounding
 - More homogeneous population
 - More accurate and precise measurements



Precision and Accuracy



■ **FIGURE 4.1**

The difference between precision and accuracy.

- Want both precision and accuracy in measuring endpoints
- Increasing sample size increases precision but not accuracy



Comparison of Clinicians and Nurse Practitioners Assessments

Sign or symptom	At enrollment	At outcome
URI	0.39	-
Increased dyspnea	0.70	0.53
Increased sputum production	0.51	0.25
Change in sputum color	0.73	0.48
Increased wheezing	.050	0.49
Increased cough	0.56	0.57
Number of symptoms (out of five)	0.49	0.47
No symptoms at end	-	0.57

Anthonisen N et al. Ann Intern Med 1987;106:196-204.

*A kappa of 0 represents chance alone and 1 represents perfect agreement



How Can a PRO Measure Help?

- Allow identification of items most important to patients
- Help define disease by accurately measuring an increase over day to day variations (more homogeneous population)
- Accurately measuring outcomes with precision (reproducible) and accuracy (items and magnitude of change) that are clinically meaningful (more precise measurements)
- Allow more frequent assessments and measurement of time to resolution of symptoms



- "It is often much worse to have good measurement of the wrong thing-- especially when, as is so often the case, the wrong thing will IN FACT be used as an indicator of the right thing--than to have poor measurement of the right thing."
- --J. Tukey



The EXACT- PRO Initiative

A collaborative approach to instrument development

Goal: Development of a new measure to capture patient experiences and outcomes of acute exacerbations in chronic bronchitis and COPD

www.exactinitiative.com





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General Statistical Considerations

- Design and analysis considerations
 - Same as for any other endpoint
 - Multiple endpoint considerations
 - Consistency with study objectives
 - Missing data considerations
 - Interpretation of findings
 - Analysis of means
 - Analysis of proportions (of responders)



The Use of Multiple Endpoints to Evaluate Treatment Effects to Support Regulatory Approval and Label Claims



Definitions

- Primary endpoint
- Co-primary endpoint (both or all primaries need to be significant)
- Secondary endpoint
- Composite endpoints
- Multiple primary composite endpoints

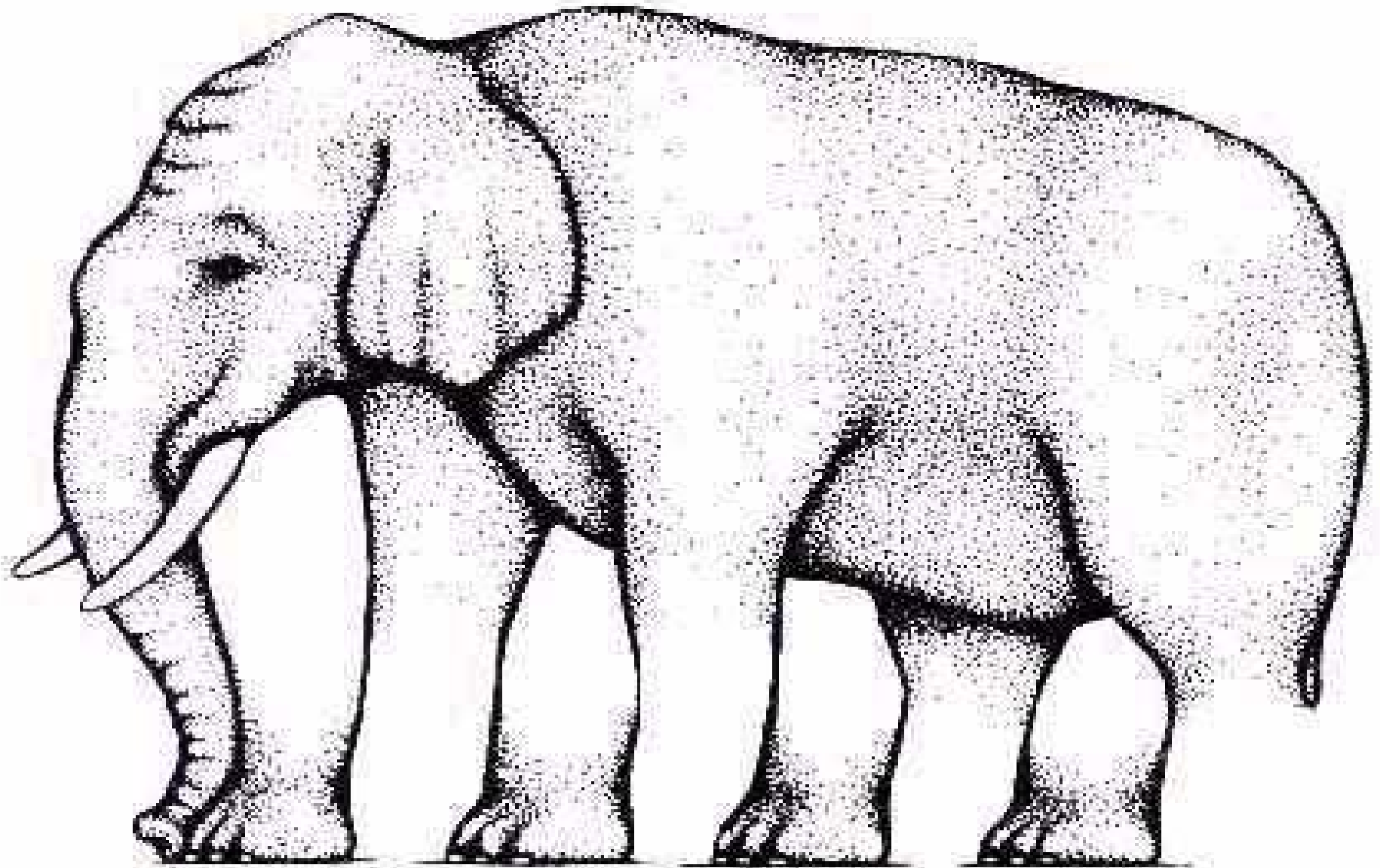


The Major Statistical Concerns

- Making an inference or a claim about one or more individual endpoints in clinical trials
- Controlling the Certainty of False Positive conclusions - Type 1 error
- Examples:
 - “closed testing” procedure
 - gate-keeper/fixed-sequence methods
 - assigning alpha to different families of endpoints
- The Loss in Statistical Power and /or increase in sample size to maintain power when there are multiple ways to “win”
- Illusion of Certainty after the fact - interpretation

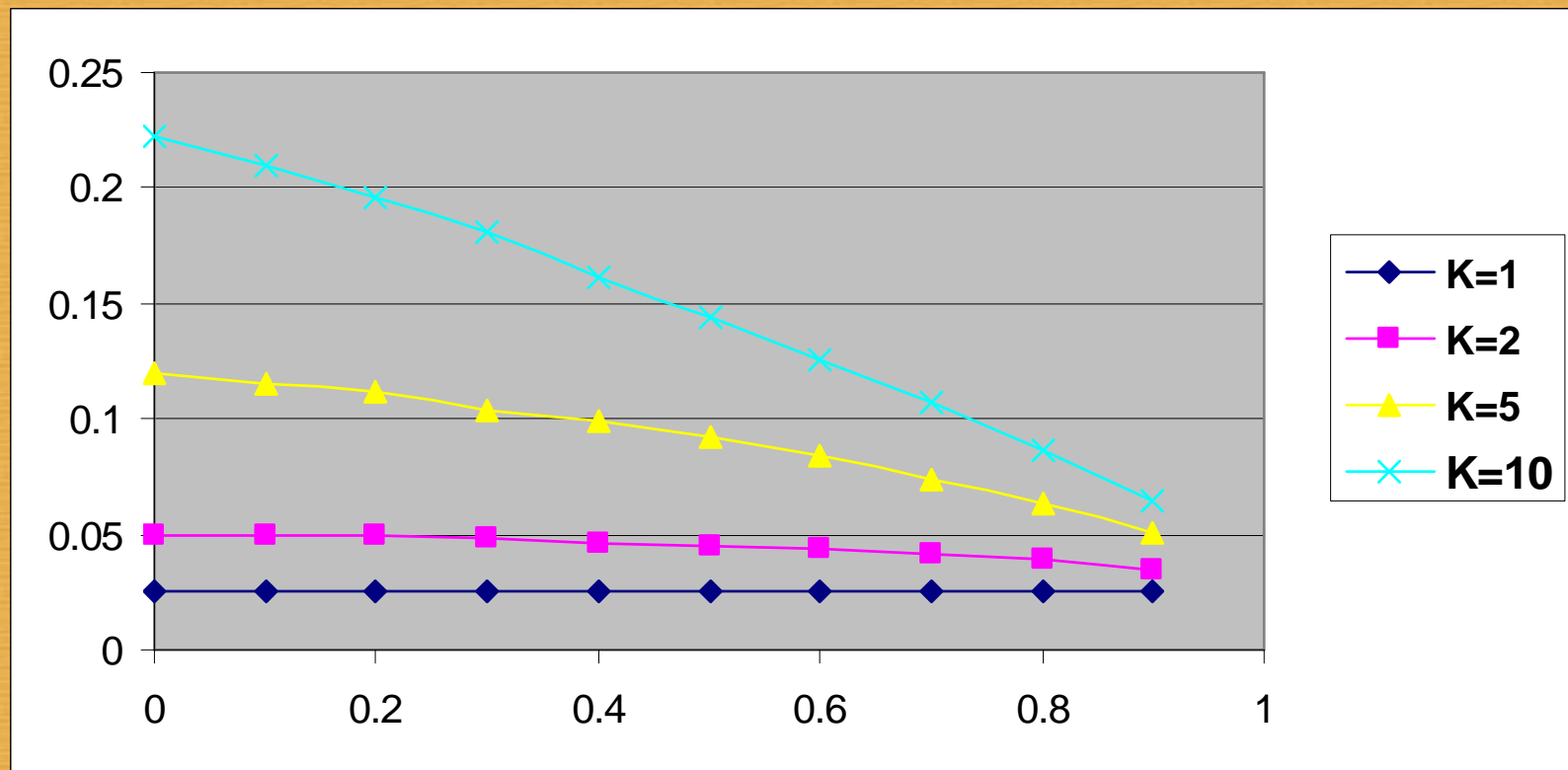


The illusion of certainty - How many legs ?



Type I error rate inflation: Win in at least one of the K endpoints Test each endpoint at level 0.025 (1-sided)

Y-axis: Type I error probability

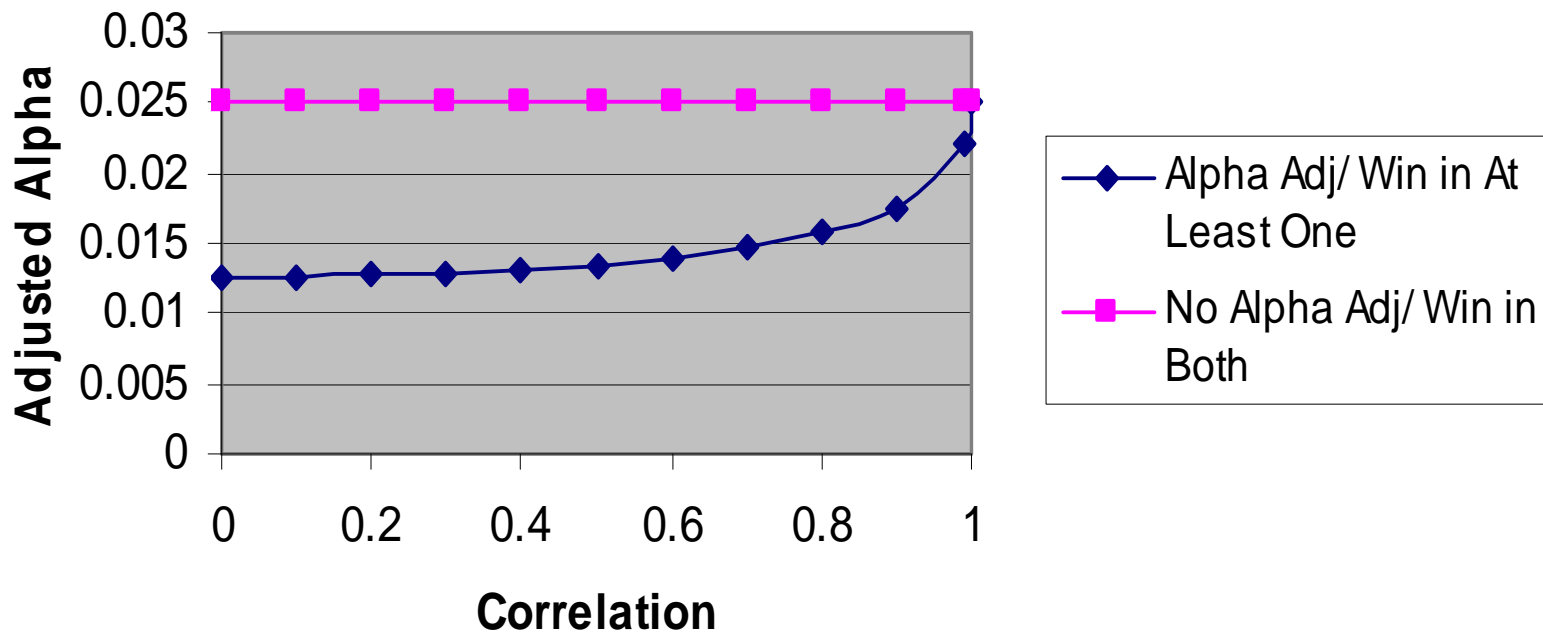


X-axis: Correlation



Adjustments in the Type I error rate Case of 2 Endpoints

**Adjustments in the Type I Error rate for the Two Win
Scenarios (1-Sided Test)**



◆ Adjustment by Sidak's method to account for correlation



Is there a hierarchy to the endpoints or their clinical importance

- Which is most important clinically
- When would the importance/ significance of a patient reported outcome be considered only after an objective outcome, or a physician reported outcome demonstrated an effect



Related Guidance on this topic

- ICH E9 'Statistical Principles for Clinical Trials'
- CPMP 'Points To Consider on Multiplicity Issues in Clinical Trials'



Missing data due to withdrawal from a trial prior to planned completion

- PRO's are very likely predictors of satisfaction with assigned treatment and with staying in a trial



Missing data

(measures of response not reported by a patient)
due to withdrawal from trial (exposure)

- Bias produced by measures only available for subjects remaining in the trial
- Informative censoring
- Design modifications to measure indicators of withdrawal reason

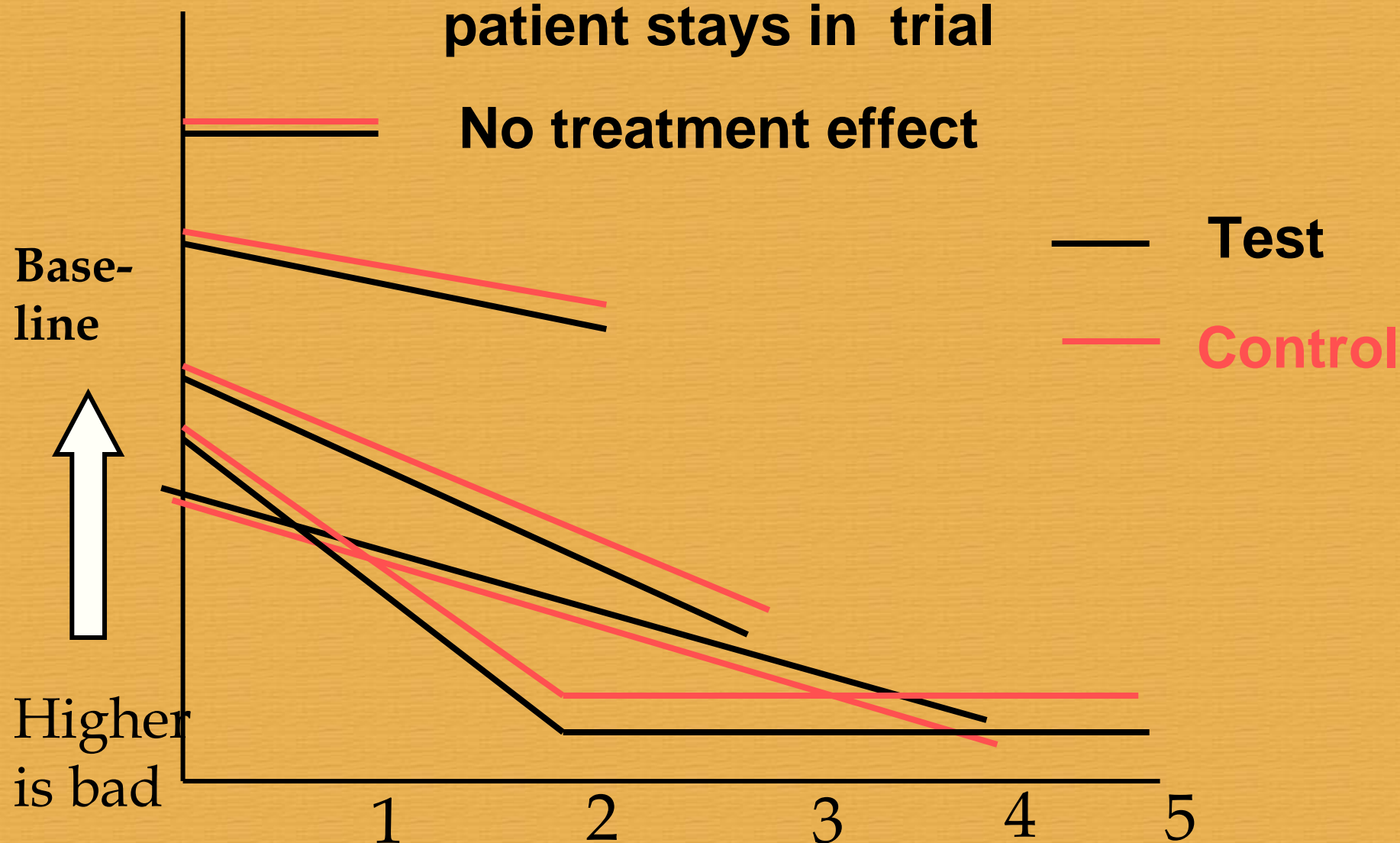


What is the problem with missing data in clinical trials ?

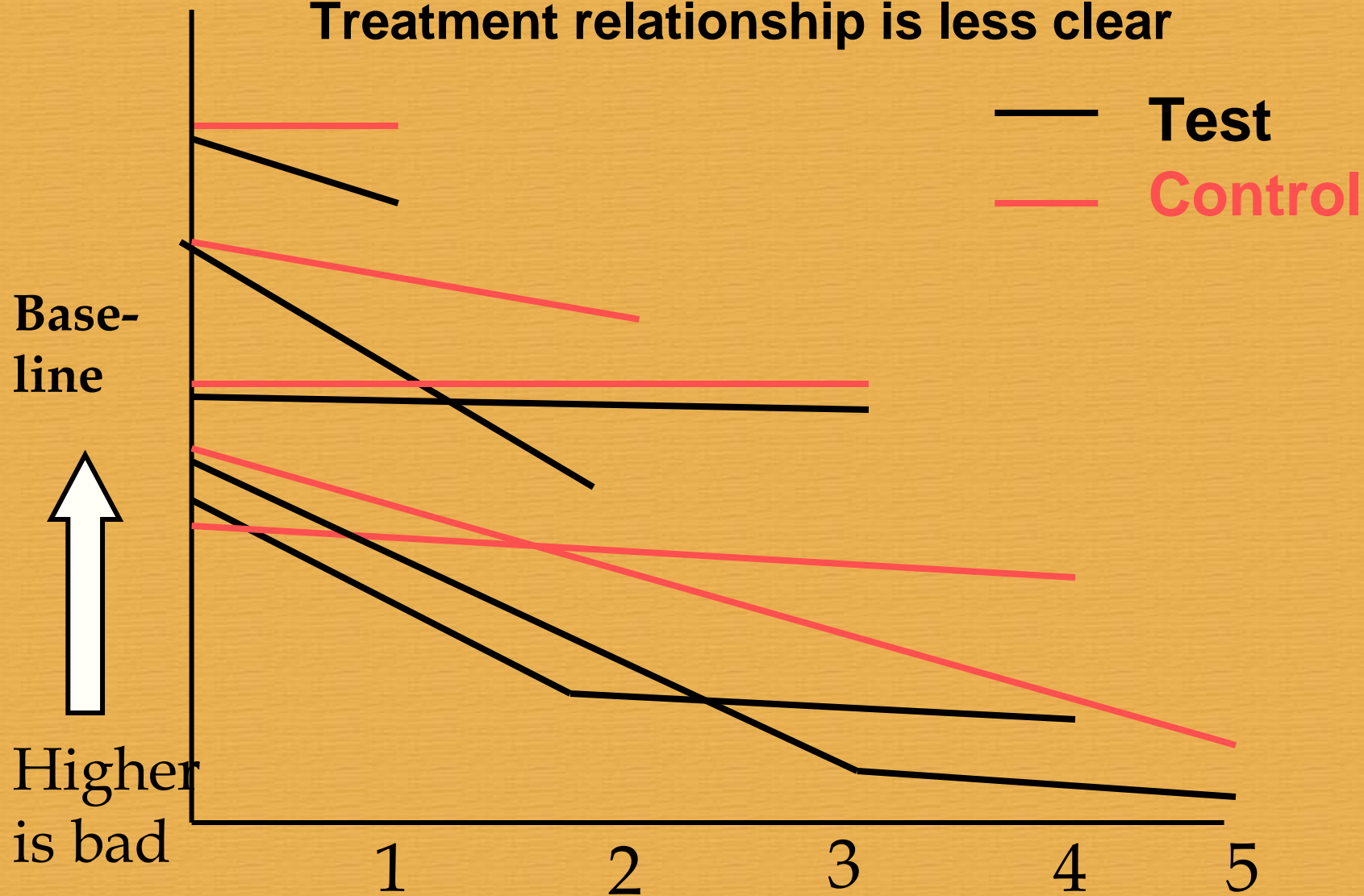
- Missing data is potentially an outcome by itself
 - Why ? - it is a surrogate for patient preference, acceptability with therapy, and it is potentially unproductive of where the subject would be in the future (where no observations are taken or available)
- Monotone missing data, the 'dropout mechanism' is almost always informative



Slope and baseline are predictive of how long a patient stays in trial



Baseline is predictive of how long a subject stays in trial
Treatment relationship is less clear



What is the “minimum important difference?”

- MID \neq Responder definition
- Is MID the smallest difference between group mean values that will be interpreted as important?
- Is it statistically useful?
 - Do we ever establish the null hypothesis to rule out a difference less than or equal to the MID?



Minimum Important Difference (MID) - A study planning tool

- The smallest difference between treatment arm means in a clinical trial that will be interpreted as important
- Should we establish the null hypothesis to rule out a difference less than or equal to the MID
- The distribution of responses between treatment groups may be more informative



MID is often used to sample size an RCT based upon the assumed mean difference between the groups

Difference in mean response between treatment groups is a difference of differences
VS

Differences within an individual - responder definitions

Interpreting treatment effects



Is there a better idea or more a more intuitive idea ?

- A comparison of the distribution of individual responses between treatment groups may be more informative
- But, deciding upon the cutoff for a response or a responder is not simple - may need evaluation of minimum change an individual can perceive as beneficial



A Responder Endpoint from Multiple Endpoints - “Clinical Win”

Rheumatology Example (ACR20):

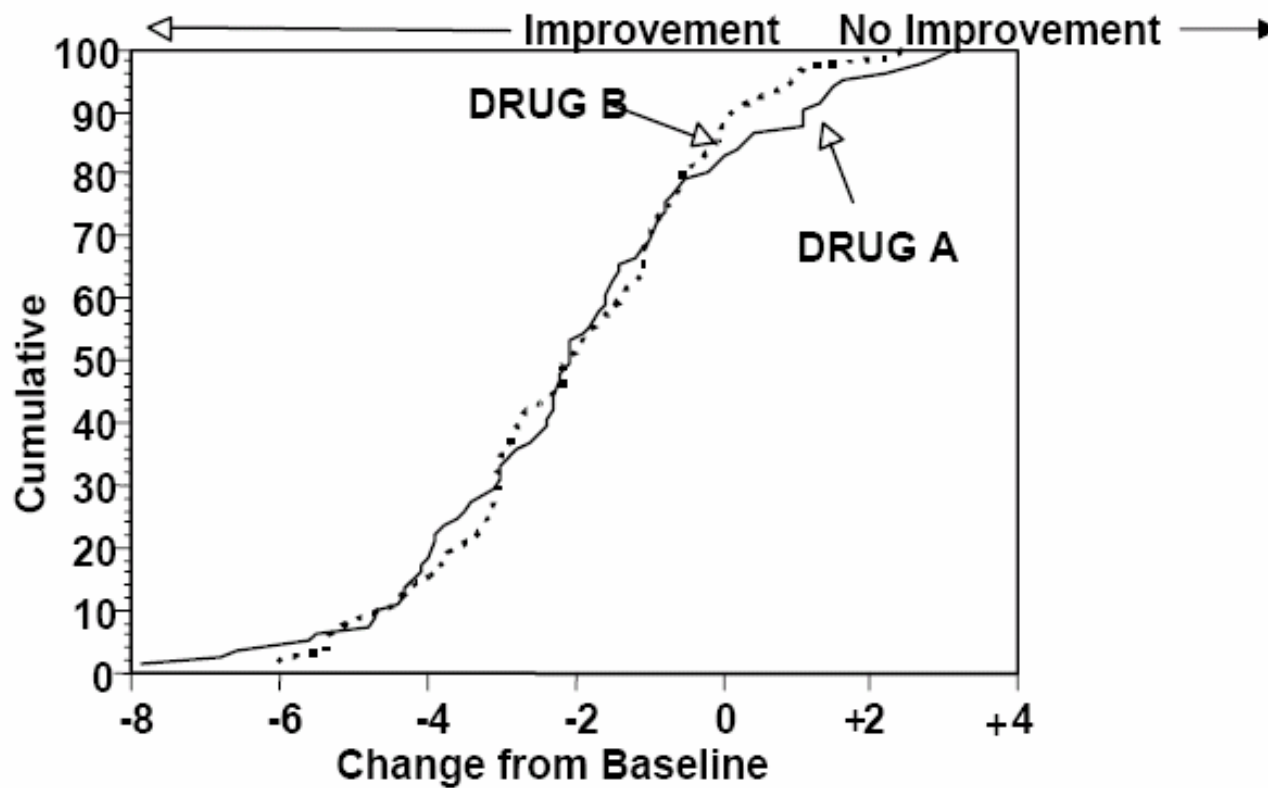
- Required:
 - at least 20% improvement in tender joint count
 - at least 20% improvement in swollen joint count
- Plus at least 20% improvement in 3 out of the 5
 - patient pain assessment
 - patient global assessment
 - physician global assessment
 - patient self-assessed disability
 - acute phase reactant (ESR or CRP)

Disease-drug process => near homogeneity of treatment effects in majority of endpoints => ACR20 is a sensible responder endpoint



Cumulative Distribution Plot

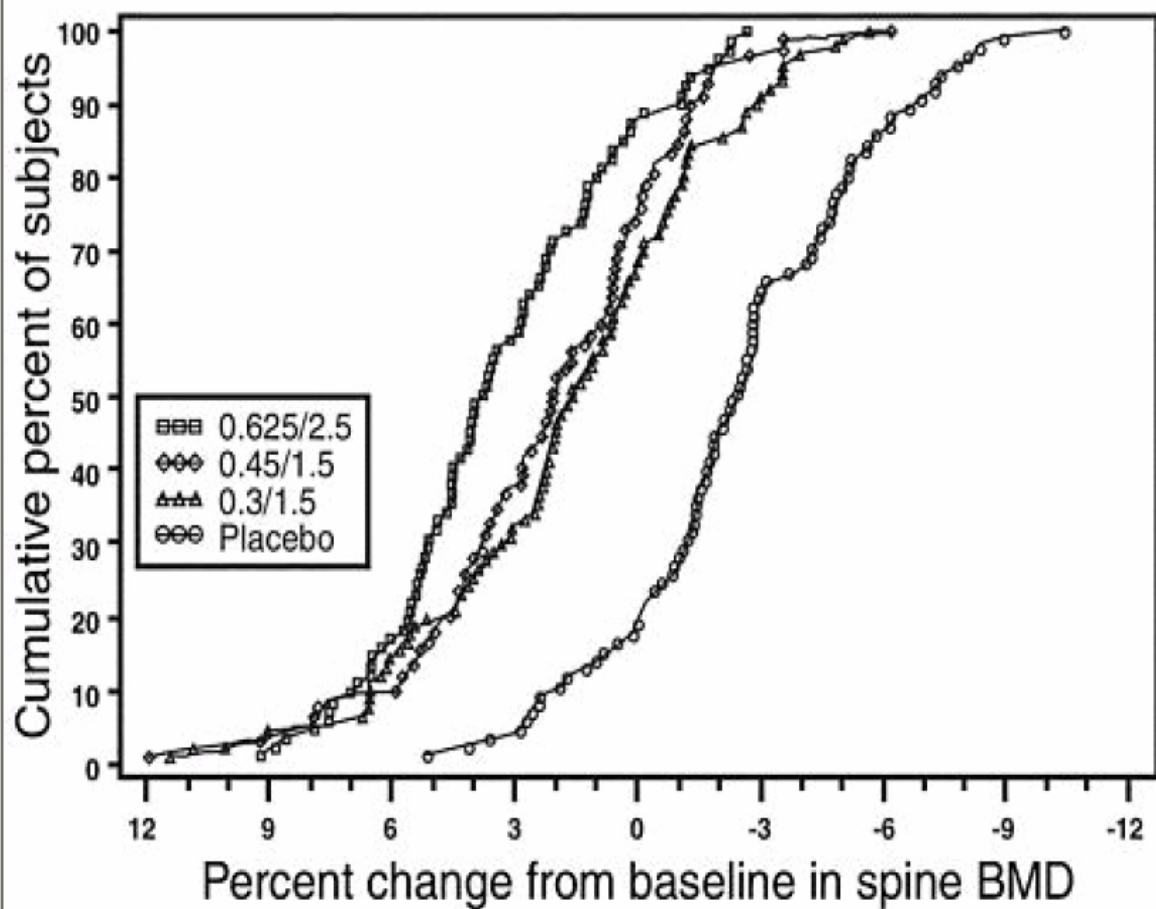
Cumulative Distribution Plot of Change From Baseline for Study 1



This graph shows the percentage of subjects (y-axis) attaining a change from baseline less than or equal to the value on the x-axis. A curve that shifts to the left indicates a better response.

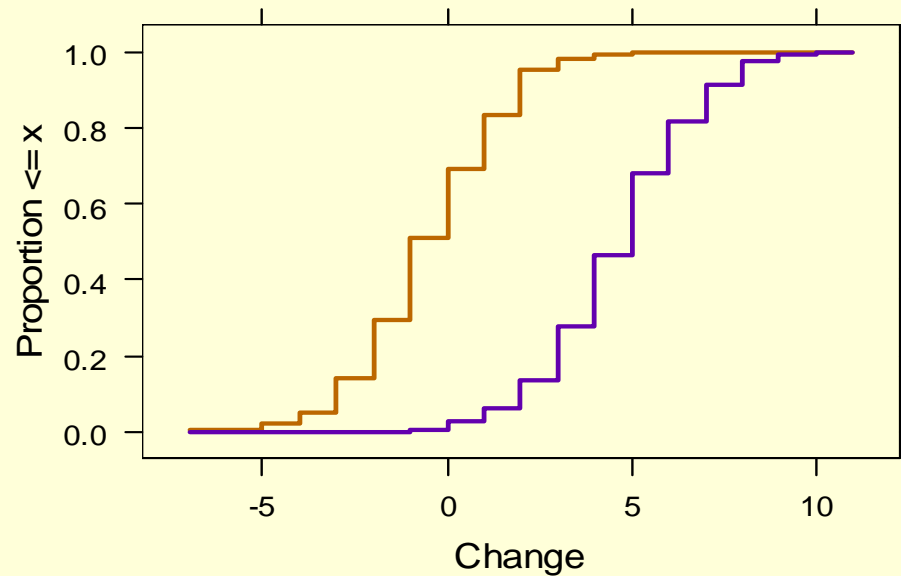
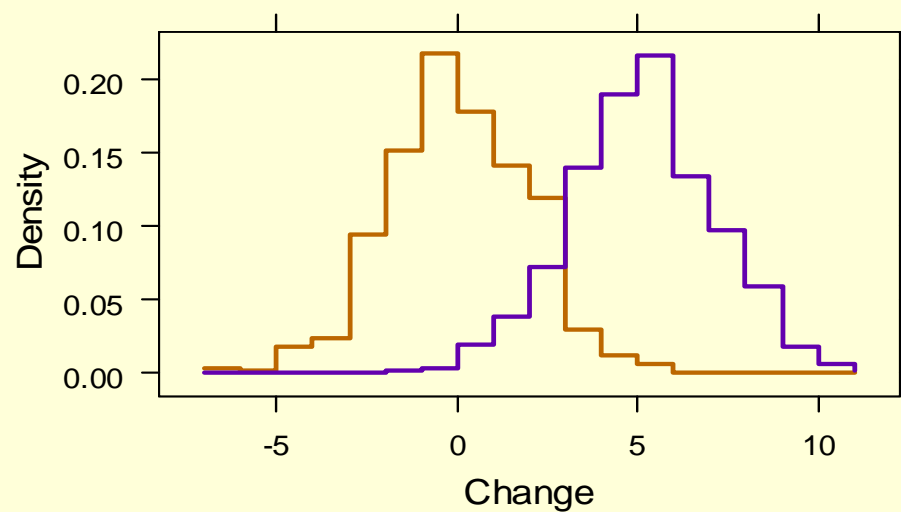


FIGURE 3. CUMULATIVE PERCENT OF SUBJECTS WITH CHANGES FROM BASELINE IN SPINE BMD OF GIVEN MAGNITUDE OR GREATER IN PREMARIN/MPA AND PLACEBO GROUPS

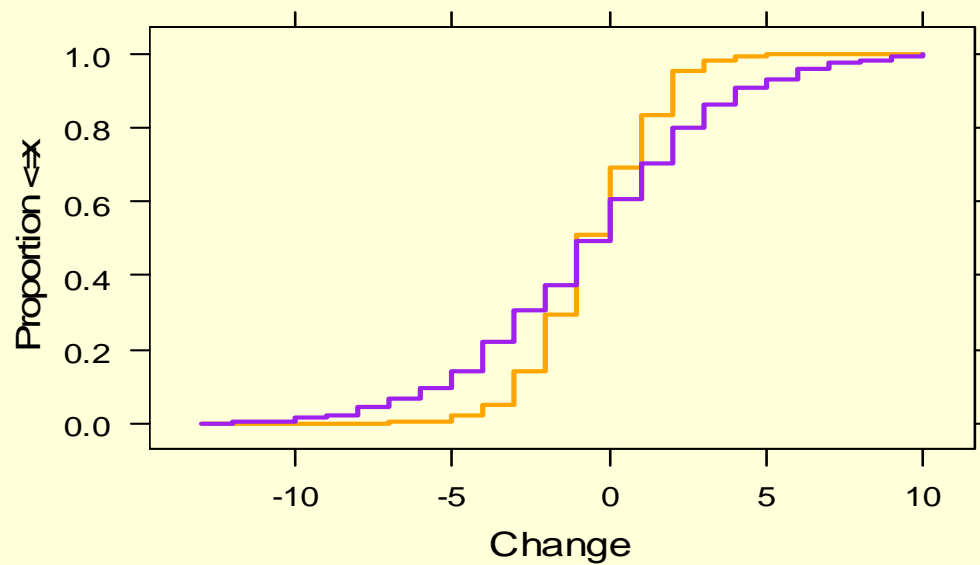
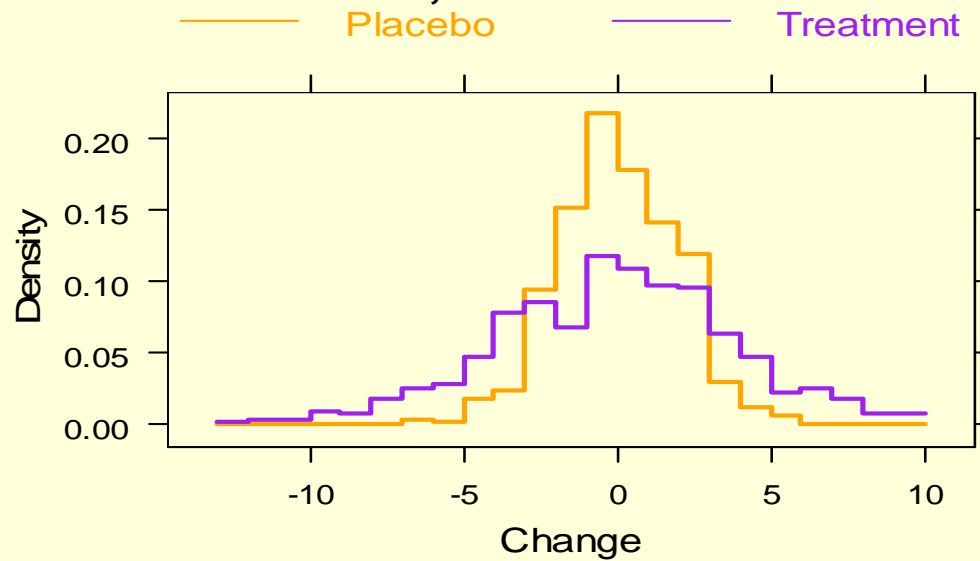


Same Variance, Shift in Mean

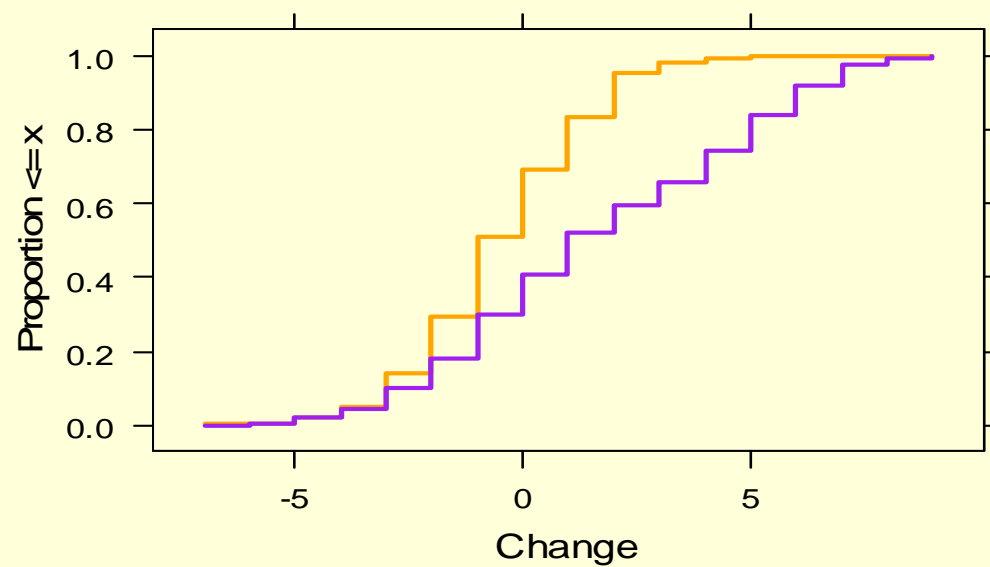
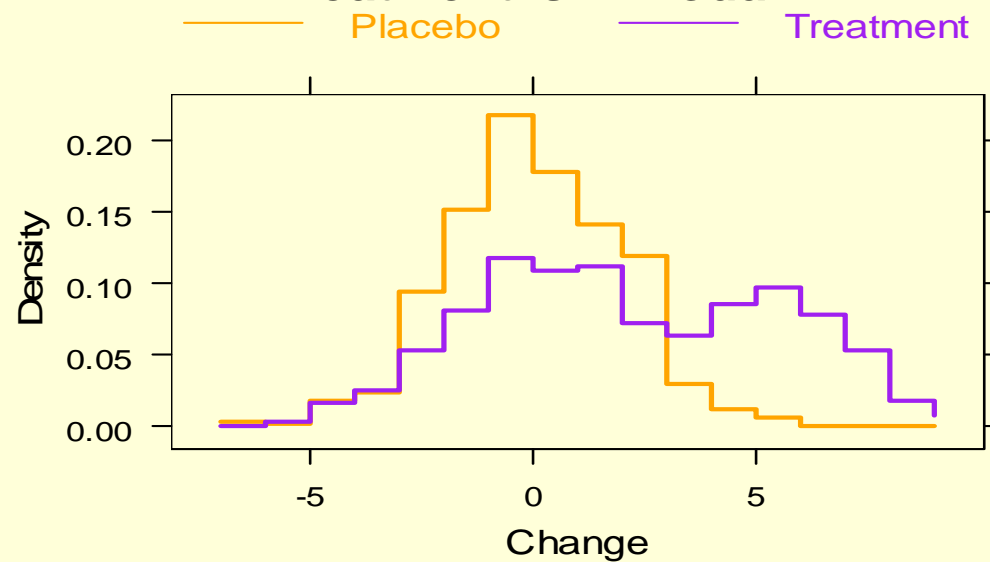
— Placebo — Treatment



Same Mean, Different Variance



Treatment is Bimodal



Final Guidance is Coming Soon!

- Expect clarification of FDA's current thinking
 - Validation after instrument modification
 - Study interpretation considerations
 - FDA's flexibility toward guidance recommendations



Summary and Discussion

- PRO ≠ QOL ≠ HRQL
- Benefit → Claim → Endpoint Model → Conceptual Framework
 - Guidance addresses medical product development, not other settings
 - Conceptual development requires patient input
 - Documentation of content validity is a review issue
- → Measurement Properties
 - Measurement properties hinge on adequate content validity
- → Study Design → Data Analysis → Interpretation
 - Same considerations as for any other endpoint

