Utilizing Statistics for Reducing Clinical Trial Costs

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Endpoints

Selecting the Primary Endpoint

- Typically, the most important determinant of trial cost is sample size
- In almost all trials, sample size is powered for the primary or co-primary endpoints
- Select carefully and measured optimally
- FDA typically requires a **clinically meaningful effect,** not only statistical significance
- This frequently leads to the Agency requiring a **responder analysis**

Responder Endpoint Examples

- Typically (with exceptions), *Responder endpoints* dichotomize continuous scales into “response” and “nonresponse”
- Examples:
  - Wound Healing: Complete closure = response; otherwise, non-response
  - Weight loss: Reduction of at least 10% at 1 year = response
  - Kidney transplant: Delayed graft function (DGF) = non-response (usually defined as need for dialysis during first week; an “exception”)
- Statistical analysis of responder analysis:
  - Comparison of response rates between arms or
  - Comparison of response rate to a specified performance goal (PG)

Responder Analysis: Advantages & Disadvantage

- Advantages
  - Simple to understand and analyze
  - Clinically meaningful if threshold is appropriately defined (e.g. by MCID)
- Disadvantages:
  - **Usually increases sample size by 30% to 50%** relative to continuous endpoint (on rare occasions, increases power ➔ check)
  - Threshold often arbitrary; not necessarily clinical meaningful

(1) Select continuous endpoint wherever possible

Maximizing Response and Optimizing Accuracy

- Even in Responder Analysis there may be a choice of threshold
- Examples:
  - Treating stenosis: 50% or 70% in evaluating treatment success
  - Diagnostics: Dichotomizing continuous score via optimal cutoff

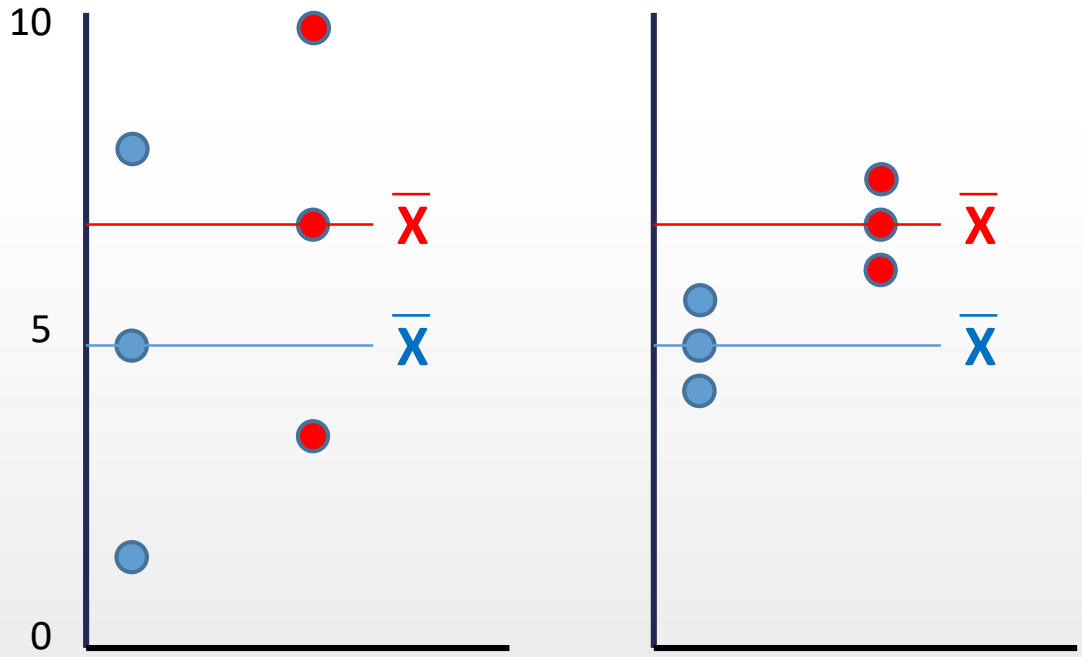
Where possible given the indication:

(2a) Intervention: Select cutoff maximizing treatment Vs. control difference

(2b) Diagnostics: Select cutoff yielding accuracy to meet label's requirement

Effect Size

Simple Analysis of a Continuous Variable



$$t = \frac{\bar{X}_1 - \bar{X}_2}{S_{\bar{X}_1 - \bar{X}_2}} = \frac{Difference\,between\,arms}{(Some\,measure\,of\,variation)/\sqrt{N}} = \frac{Difference}{Standard\,Error}$$

Goal ⇨ Maximize t
(Minimize P-Value)

Aim of Continuous Endpoint Analysis

$$t = \frac{Mean2 \ - Mean2}{(\text{Standard } Deviation) \ /\sqrt{\text{N}}}$$

- Maximize t by one or more of the following:
  - Increase difference between *Mean1* and *Mean2*
  - Decrease variation
  - Increase sample size
- Our objective is to increase power without increasing N; we ignore the option of increasing sample size

Increasing Difference between Arms

- **(3a)** Select subjects to maximize effect via inclusion/exclusion:
  - Least likely to drop out
  - Not too sick that can't be helped, not so healthy that are likely to show spontaneous recovery
  - Selection by biomarker
- **(3b)** Set trial parameters to maximize effect. Examples:
  - Set time point where difference is greatest
  - Select subjects that are least likely to show placebo effect (e.g. longer screening period to exclude "volatile" subjects)

Optimize subject characteristics, time of measurement and labeling

Variability Reduction

Decreasing Noise (Variation)

- **(4a)** Select subjects to be homogeneous as possible via inclusion/exclusion
- **(4b)** Minimize number of sites to the degree possible
- Reduce measurement error (noise):
  - **(4c)** Measure with good accuracy (e.g. true $Eta^2 = 0.64$: if repeatability=0.8, $Eta^2 = 0.27$; if repeatability = 0.9, $Eta^2 = 0.42$); select optimal tool (e.g. MRI rather than CT)
  - **(4d)** Use central lab
  - **(4e)** Measure multiple times per time point
  - **(4f)** Train evaluators well and, where possible, certify
  - **(4g)** Have each subject assessed by a single evaluator

(5) Reduce Noise by Controlling for Extraneous Variables

- Baseline variables are often related to outcome. Examples:
  - Tumor size in cancer (outcome is overall-survival)
  - Baseline NIHSS in stroke (outcome mRS)
  - Gestational age at birth when treating preterm babies (outcome = survival)
- Since subjects vary on these variables, and variables are related to outcome, they cause "noise" in predicting outcome with treatment
- Such noise can be reduced by a family of procedures called *analysis of covariance*

Brennan, CK et al. The risks and rewards of covariate adjustment in randomized trials: an assessment of 12 outcomes from 8 studies. *Trials* 2014;***15***:139

Thank You!