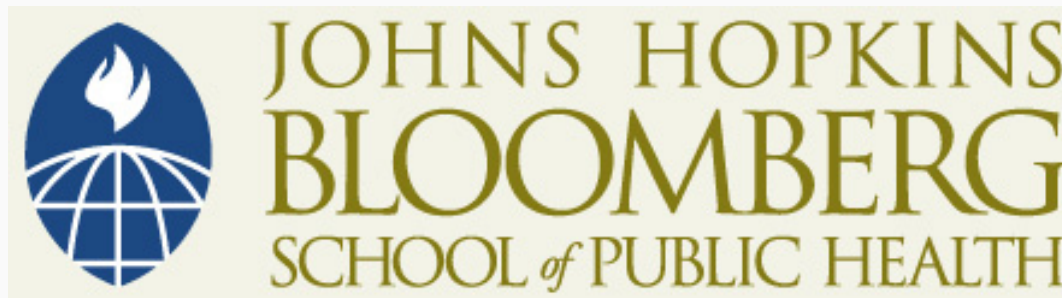


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Non-Inferiority Specification of δ

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Section A

Setting the Stage

- “Scientifically, efficacy is . . . established by demonstrating superiority to placebo . . . or showing a dose-response relationship”
- Some comparisons of an investigational product to a reference product may be intended to show the two products are . . .
 - “About the same” (equivalence)
Or the investigational product is
 - “Not much worse” than the reference product

Non-Inferiority

- A trial that compares the investigational product to an established reference product with the goal of showing “not much worse” is called a non-inferiority trial
 - ICH E9 states “a trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent” may also be called an active control trial

Active Control Trials

- Some issues
 - How much worse than the reference can be accepted?
 - Never want it to be worse than the placebo
 - Assumes reference treatment is consistently better (in repeated trials) than placebo (show efficacy consistently)
 - Ideally it should have demonstrated a high level of efficacy
 - Comparator should be widely used for relevant indication

Non-Inferiority

- Use confidence intervals for the difference between new product and control
- This shows that . . .
 - The lower limit exceeds $-\delta$ (non-inferiority) or
 - The confidence interval lies entirely within the interval $(-\delta, \delta)$ (for equivalence)
- Cannot conclude equivalence or non-inferiority by observing a non-significant test of a conventional null hypothesis

Choice of Active Control (from ICH E10)

- Prefer double blind, but it's not always possible if you have different regimens (schedule, route of administration, etc.)
- Trial must be capable of distinguishing effective treatments from less effective or ineffective treatments
- Sometimes a placebo group can be included

Assay Sensitivity (E10)

- Historical evidence of sensitivity
 - Similarly designed trials regularly distinguished effective from ineffective treatments
 - Evaluate prior to onset of trial—show that comparator product is reliably superior to placebo
 - Appropriate trial conduct—did not undermine ability to distinguish treatments
 - ▶ Must evaluate during and after the trial has been conducted: entry criteria, randomization, blinding, concomitant therapy, good compliance, low loss to follow up

E10 Summary on Assay Sensitivity

- Four steps
 1. Historical evidence determination (1.5.1.1)
 2. Trial design
 3. Setting margin—must be realistic and sufficient to provide assurance that the new product is substantially better than placebo
 4. High quality trial conduct (1.5.1.2)

Usefulness of Specific Concurrent Control Types in Various Situations

	Type of Control							
Trial objective	Placebo	Active non-inferiority	Active superiority	Dose response (D/R)	Placebo + active	Placebo + D/R	Active + D/R	Placebo + active + D/R
Measure <i>absolute</i> effect size	Y	N	N	N	Y	Y	N	Y
Show existence of effect	Y	P	Y	Y	Y	Y	Y	Y
Show dose-response relationship	N	N	N	Y	N	Y	Y	Y
Compare therapies	N	P	Y	N	Y	N	P	Y

Y = yes, N = no, P = possible, depending on whether there is historical evidence of sensitivity to drug effects

The Problem

- How to show the new product has identical efficacy to the standard (active control)?
- Answer: WE CAN'T!
- SOLUTION???



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Section B

The Solution

The Solution

- How to show the new product has identical efficacy to the standard (active control)?
- Answer: WE CAN'T!
- SOLUTION: allow some potential difference in efficacy: δ (delta)

What Is δ ?

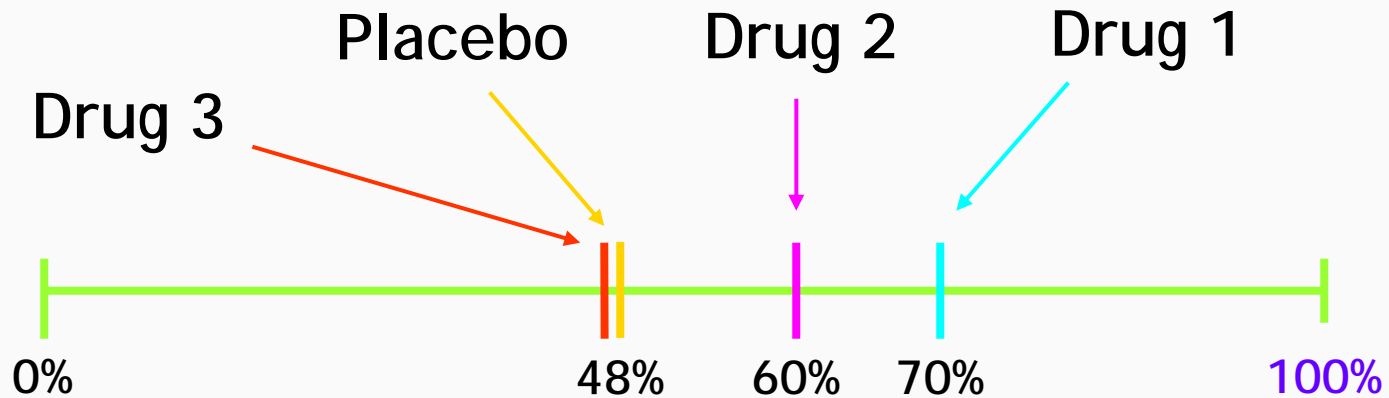
- The largest clinically acceptable difference
- Should be smaller than differences observed in superiority trials of active comparator

Goals of Non-Inferiority Trials:

- Indirectly determine if the new product is better than placebo
- Directly determine if the new product is similar to the active control
- Choose δ to assure that both of these goals are met

Concern of Potential “Bio-Creep”

- Trials over time used progressively less effective control arms
- Example: if δ of 20% is used



Committee for Proprietary Medicinal Products (CHMP)

- Published “guidance on evaluation of new anti-bacterial medicinal products” in 1997
- $\delta = 10\%$ for “common non-serious infections”
- Smaller for very high cure rates
- Based on “minimum clinically relevant difference”
- Justified in protocol

ICH-E10 Says . . .

- Non-inferiority design “is appropriate and reliable only when the historical estimate of [the] drug effect size can be well supported by reference to results of previous studies of the control drug”

Principles from E10

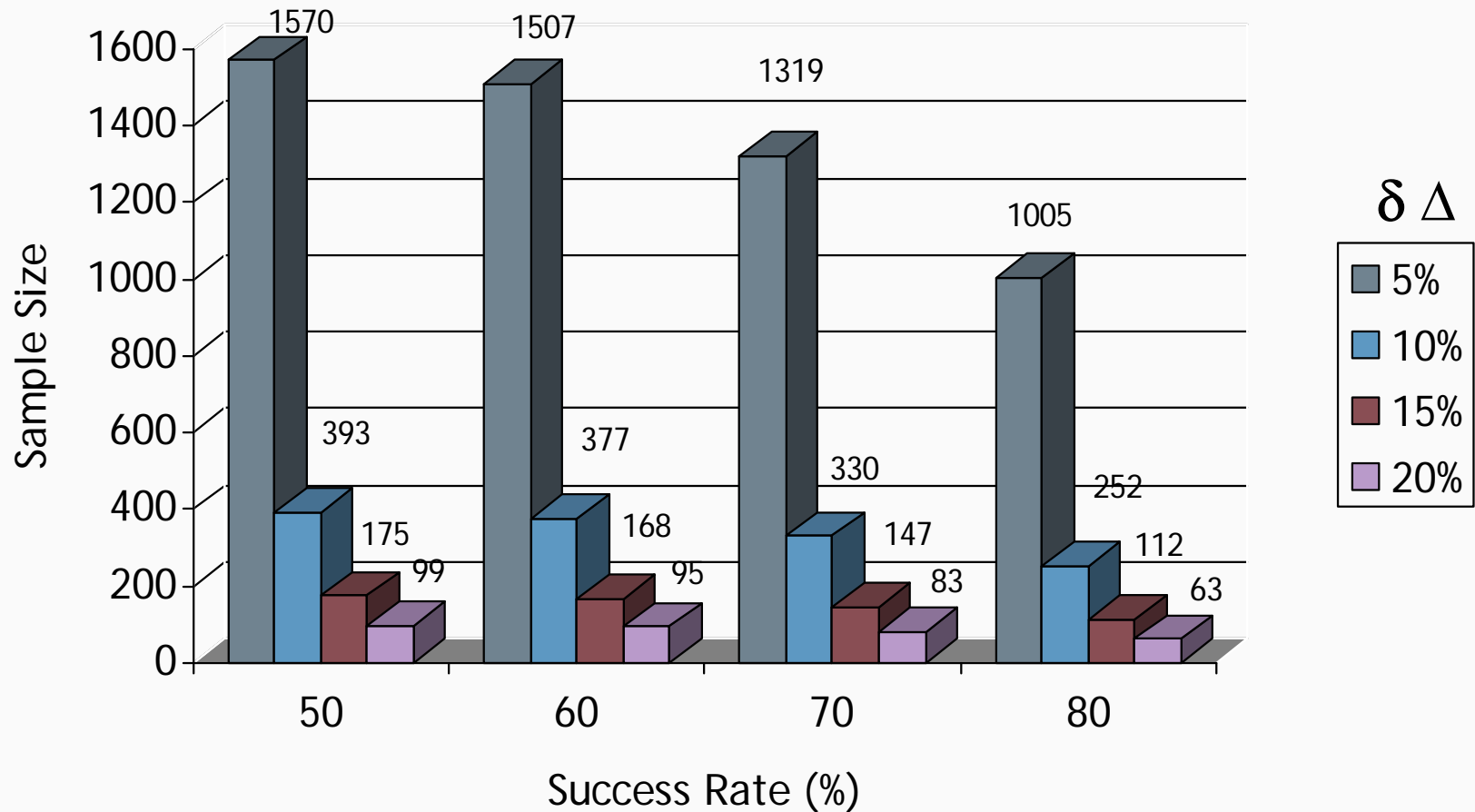
- δ “based on both statistical reasoning and clinical judgment”
- δ cannot be larger than the advantage the “active drug would be reliably expected to have compared with placebo in the setting of the planned trial”
- Usually choose δ to be even smaller to ensure some clinically acceptable treatment benefit was maintained

Clinical Trial Implications:

- For a given delta (δ), the lower the success rate, the larger the sample size
- For a given success rate, the smaller the delta (δ), the larger the sample size

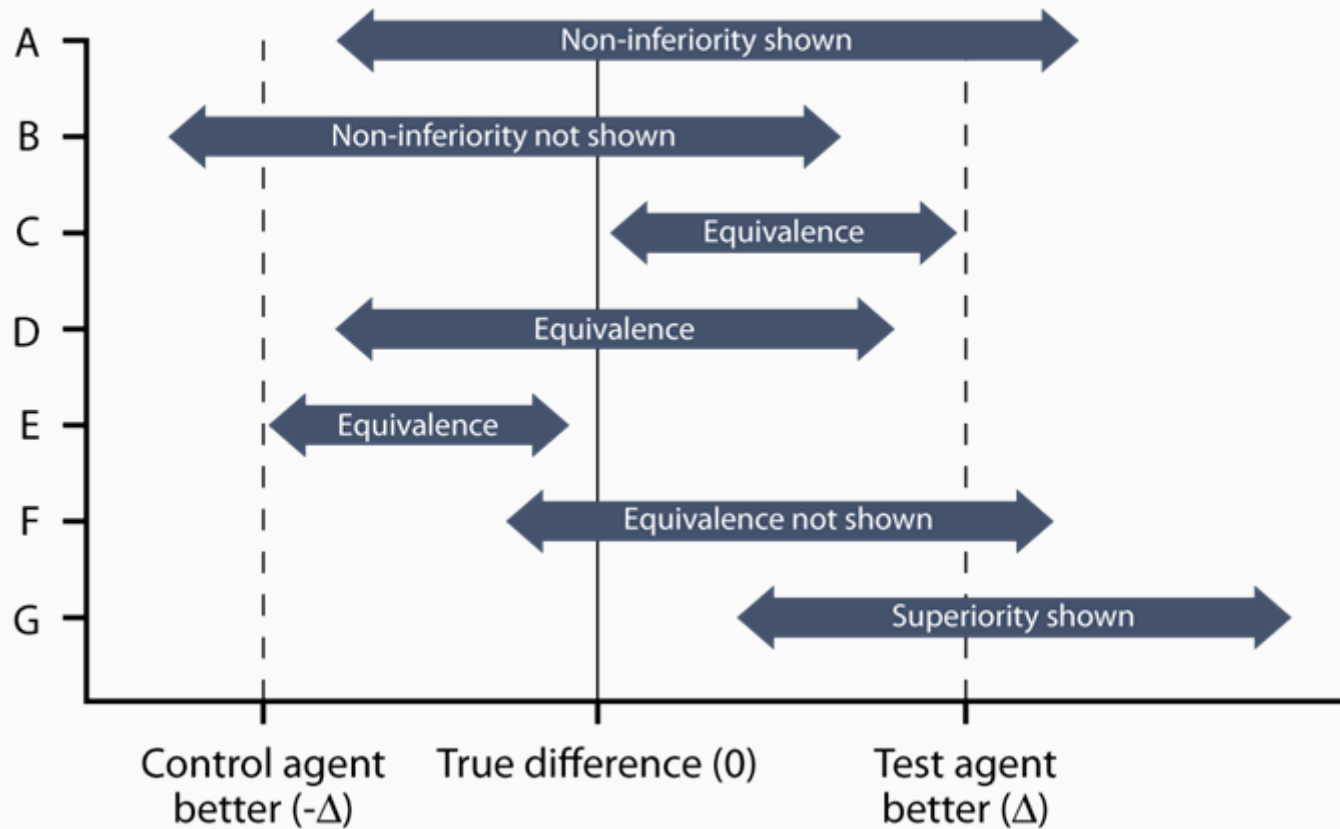
Clinical Trial Implications

- Clinical trial implications: sample size per arm to achieve 80% power



Confidence Interval Approach to Analysis

Confidence Interval Approach to Analysis of Equivalence and Non-inferiority Trials



Adapted by CTLT from Pater, *Curr Cont Trials in Cardiovas Med*, (2004).



In the Next Lecture We'll Look at . . .

- Multi-regional studies
 - Reasons
- Bridging studies
 - Intrinsic and extrinsic factors