Issues on Design of Clinical Trials

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Outline

- Why do clinical trials?
- Types of hypotheses
- Design of clinical trials
- Sample size & power considerations
- How do we minimize bias?
- Concluding remark

Why do clinical trials?

- To answer a clinical problem
- To gain new knowledge about a new or established treatment
- To support a “claim”

- For gaining government regulatory approval
- For marketing a drug, device, or technique

Principles of clinical trials

- Ethics
- Scientific validity and integrity

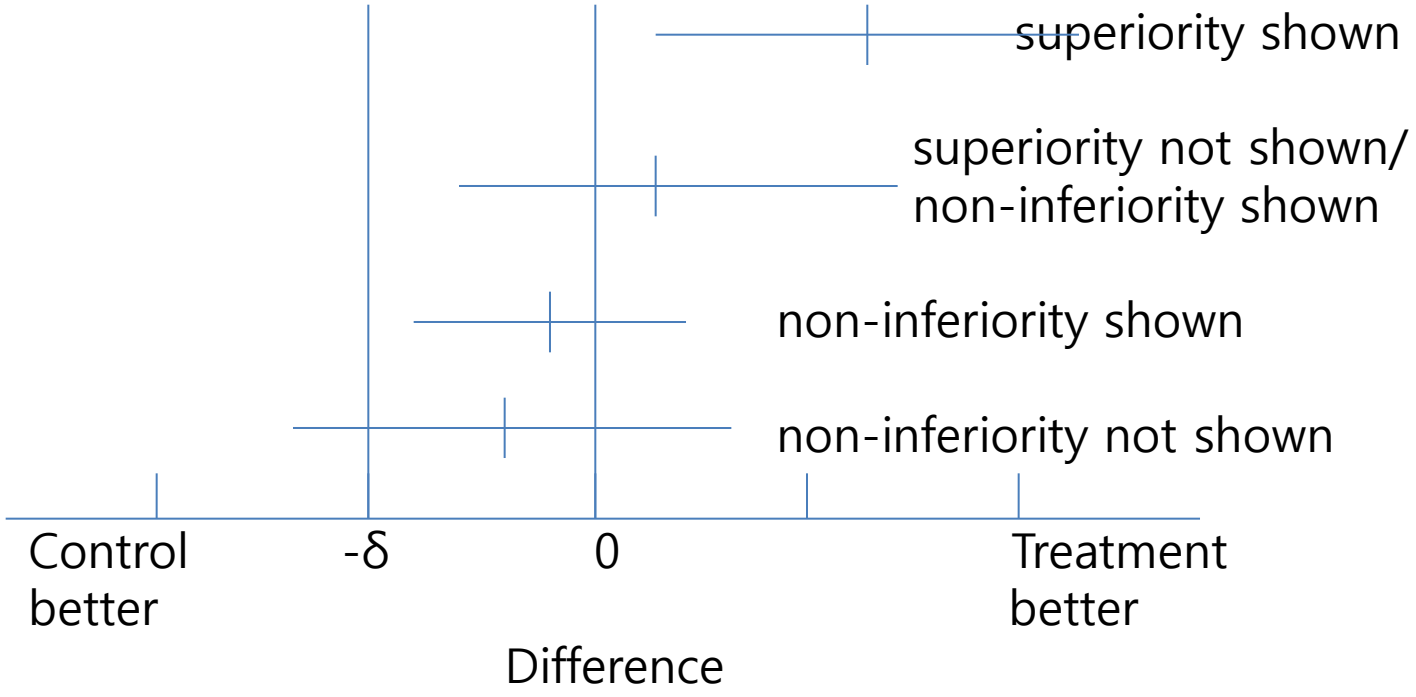
What is step one?

- Start with a hypothesis

- Must be in the form of a statement
- The question must be “answerable”
- Choose the outcome you wish to measure

Types of hypotheses

Superiority
Non-inferiority
Equivalence



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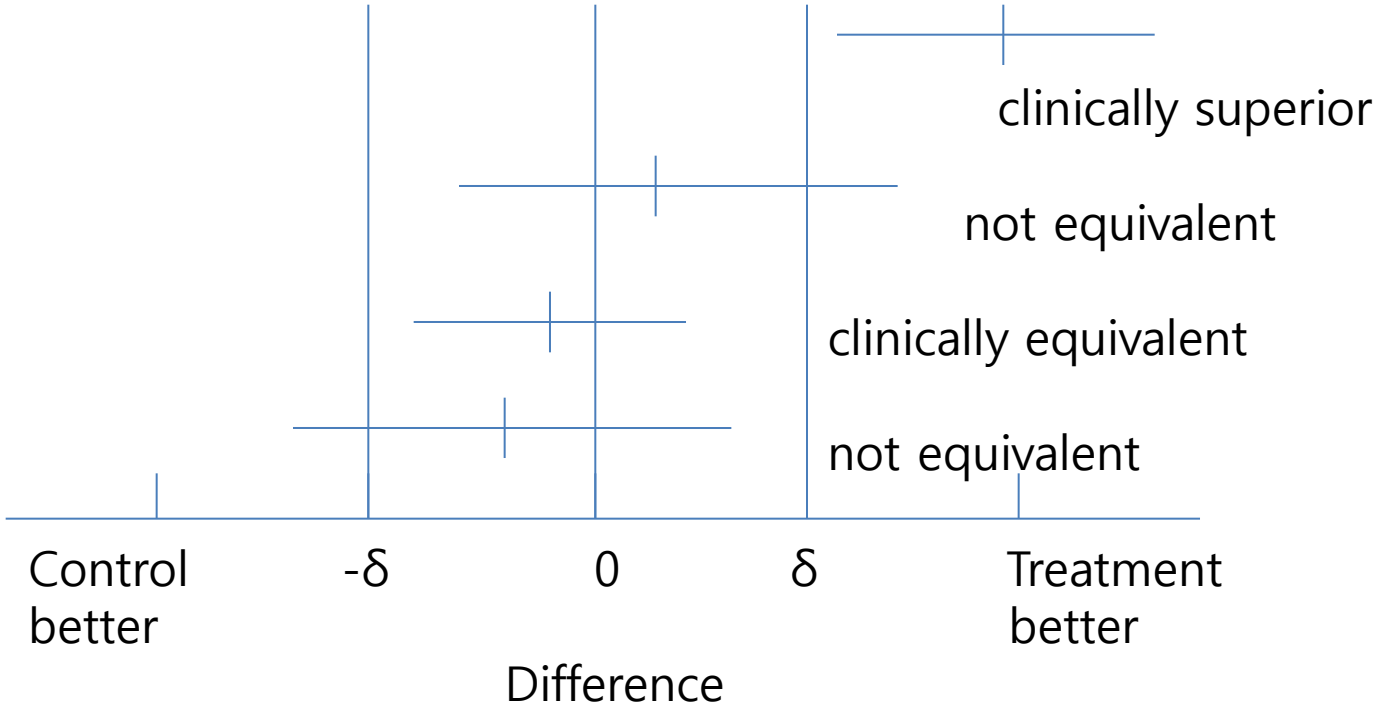


Non-Inferiority Challenges

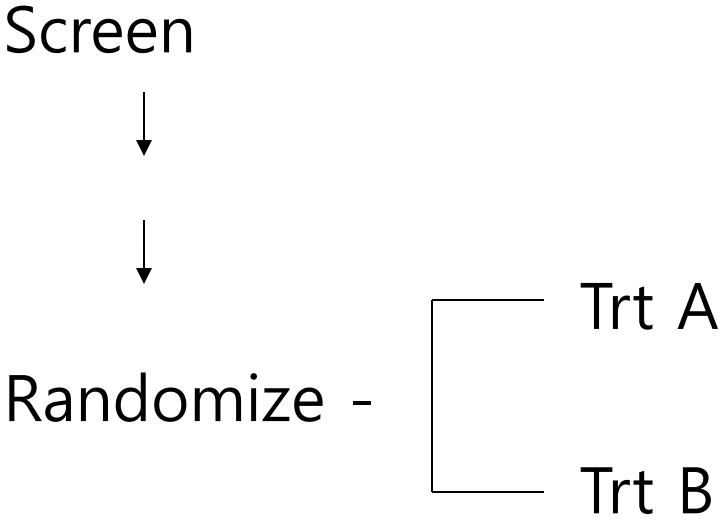
- Requires high quality trial
- Treatment margin somewhat arbitrary

Commonly used designs

- Parallel design
- Factorial design
- Cross-over design
- Group sequential design

etc

Parallel Design



- H_0: A vs. B
- Advantage
  - Simple, General Use
  - Valid Comparison
- Disadvantage
  - Few Questions/Study

Factorial Design

- Schema

		Factor I	
		Placebo	Trt B
Factor II	Placebo	N/4	N/4
	Trt A	N/4	N/4

A vs. Placebo

B vs. Placebo

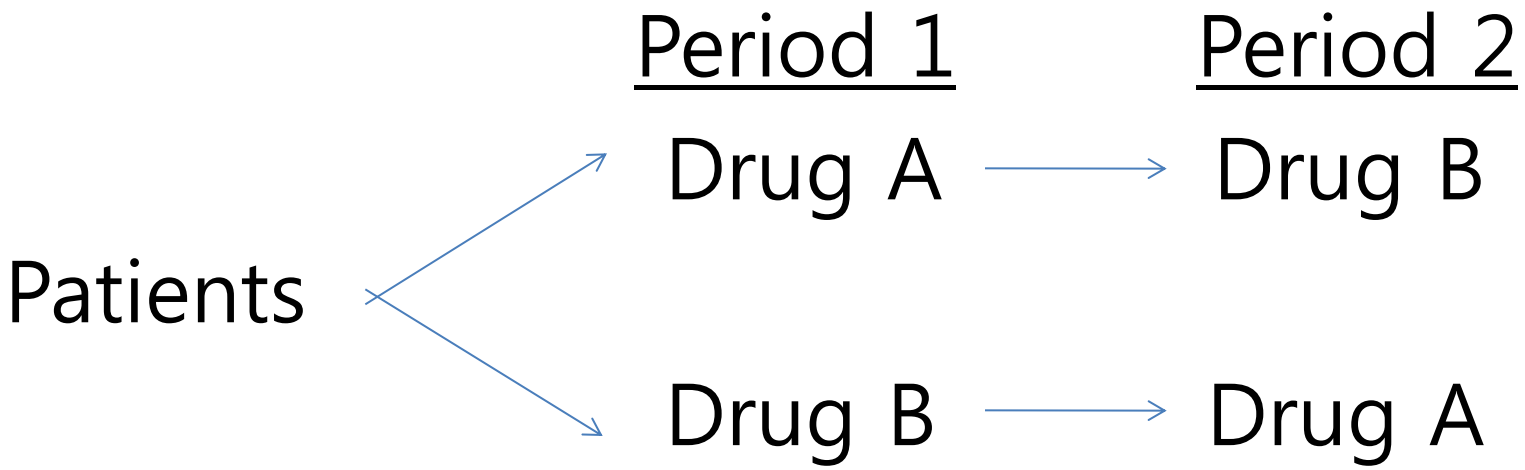
Factorial Design

- Advantages
  - Two studies for one
  - Discover interactions
- Disadvantages
  - Test of main effect assumes no interaction
  - Often inadequate power to test for interaction
  - Compliance
- Examples
  - Physicians' Health Study (PHS) *NEJM* 321(3):129-135, 1989.
  - Final report on the aspirin component
  - Canadian Cooperative Stroke Study (1978) *NEJM* p. 53

Crossover Design

- Each patient receives both treatments.
- Order of treatment is randomized.
- Comparison is “within” patients not “between” patients.

Crossover Design



Crossover Design

Patients must complete both arms.
Drug must be short acting.

- Advantages:
  - Sample size reduced.
  - Allows a preference question

- Disadvantages:
  - Possible carry-over effect
  - Possible period effect (time)

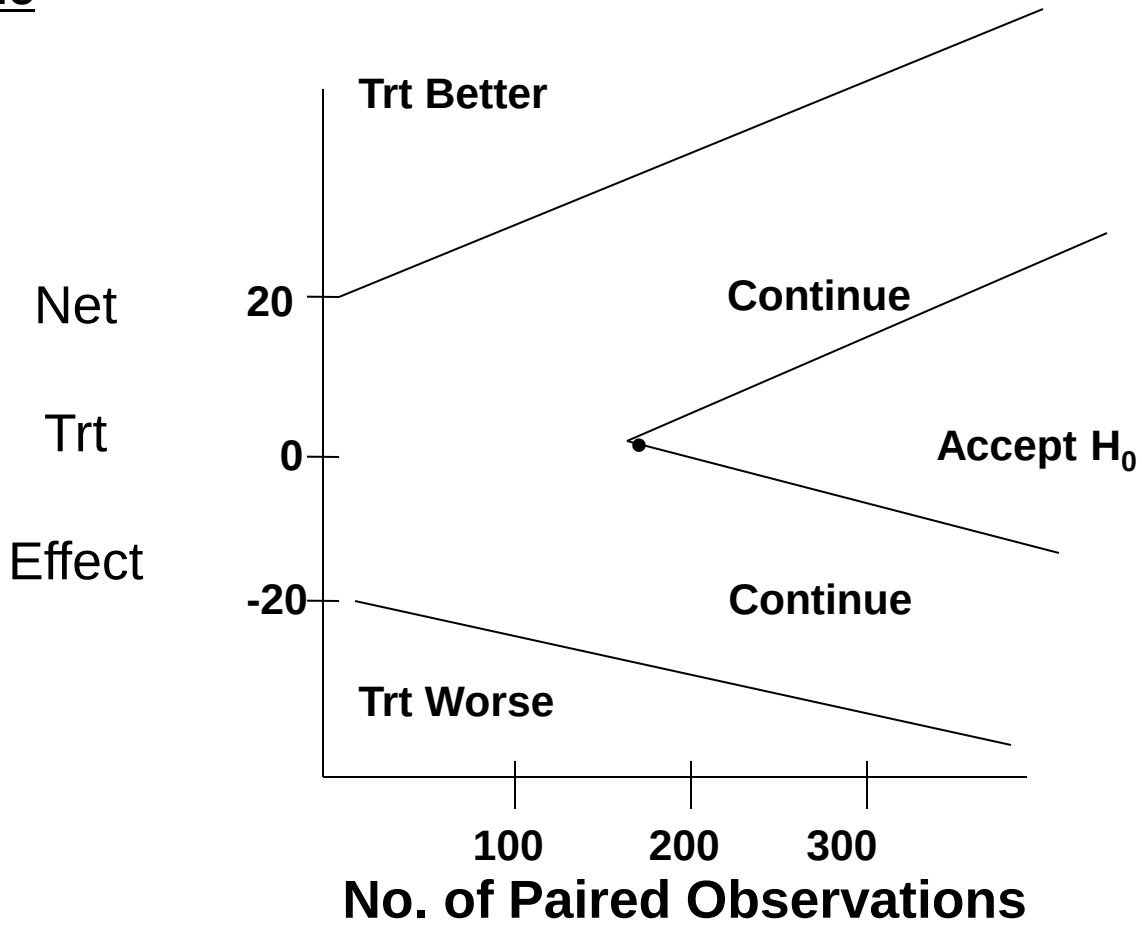
Sequential Design

- Continue to randomize subjects until H_0 is either rejected or "accepted"
- A large statistical literature for classical sequential designs
- Developed for industrial setting
- Modified for clinical trials

  (e.g. Armitage 1975, Sequential Medical Trials)

Classical Sequential Design

- **Continue to randomize subjects until H_0 is either rejected or "accepted"**
- **<u>Classic</u>**



What is minimum number of patients to conduct a clinical trial?

- Sample size & power calculation

Primary objective & primary endpoint

Definition of primary objective & primary endpoint is required.

Primary endpoint	Test method
Categorical data	Chi square test
Continuous data	T test/ ANOVA
Survival data	Log rank test

Sample size calculation (1)

$P_C = 0.10$
$P_T = 0.05$

$P_C - P_T = 0.05$ (risk reduction rate: 50%)

What is the required number of patients to detect 50% reduction of mortality rate ?

Sample size calculation (2)

$$n_C = r\, n_T$$

$$n_C = \frac{\frac{r+1}{r}\left(z_{\alpha/2} + z_{\beta}\right)^2 \bar{p}\,(1-\bar{p})}{\left(p_1 - p_2\right)^2}$$

$$\bar{p} = \frac{p_1 + p_2}{2}$$

Sample size calculation (3)

Effect size	Mortality rate		Alpha	Power	n per group
	Treatment	Control			
5%	5%	10%	0.05	80%	435
5%	5%	10%	**0.01**	80%	**647**
4%	6%	10%	0.05	**58%**	435
3%	7%	10%	0.05	**35%**	435
4%	6%	10%	0.05	80%	**721**
3%	7%	10%	0.05	80%	**1,356**

Sample size calculation (4)

Change	Sample size
alpha (type I error rate) ↓	↑
Power ↑	↑
Effect size ↑	↓
Effect size ↓	↑
Proportion near to 50%	↑

What is a clinical trial's greatest enemy?

- Bias

How do we minimize bias?

- Make sure groups are equivalent

=> **Randomization**

- Standardize outcome assessment

=> **Blinding**

- Unbiased data analysis

=> **ITT principle**

Concluding remark

It is highly recommended to co-work with biostatistician from the early stage of planning clinical trials.

Thank you for your attention.