Lecture 4

Sample Size Calculation in Clinical Research

Overview

- Basic Considerations
- Comparing Means
- Comparing Proportions
- Comparing Time-to-event Data
- Genomics
- Summary

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Basic Considerations

- Type of Sample Size Calculation
- Type I error and Power
- Hypotheses
- Study Designs
- Information required
- Practical Issues

Type of Sample Size Calculation

- Sample Size Calculation/Estimation or Determination
- Sample Size Justification
- Sample Size Re-estimation
- Sample Size Adjustment

Type I Error and Power

Sample size is usually selected for achieving a desired power (say 80% chance of correctly detecting a clinically meaningful difference) at a pre-specified significance level (say 5%)

Hypotheses Testing

- Test for Equality
- Test for Non-inferiority
- Test for Superiority
- Test for Equivalence

Test for Equality

- It is a commonly employed approach for demonstration of the efficacy and safety of a drug product
  - First, to show that there is a difference between the test drug and the control (e.g., placebo control)
  - Then, to demonstrate that there is at least 80% power for correctly detecting a clinically meaningful difference if such a difference truly exists

Test for Non-inferiority

- Purpose
  - To show that the test drug is as effective as a standard therapy or an active agent
- Situations where it is applicable
  - The test drug is less toxic
  - The test drug is easier to administer
  - The test drug is less expensive

Test for Non-inferiority

- Hypotheses
  - Null hypothesis: The test drug is inferior to the standard therapy
  - Alternative hypothesis: The test drug is as effective as the standard therapy
- The concept is to reject the null hypothesis and conclude that the difference between the test drug and the standard therapy is less than a clinically meaningful difference and hence the test drug is as effective as the standard therapy.

Test for Superiority

- Purpose
  - To show that the test drug is superior to a standard therapy or an active agent
- Remark
  - In practice, it is not preferred unless there is some prior knowledge regarding the test drug

Test for Superiority

- Hypotheses
  - Null hypothesis: There is no clinically meaningful difference between the test drug and the standard therapy
  - Alternative hypothesis: The test drug is superior to the standard therapy
- The rejection of the null hypothesis suggests that the difference between the test drug and the standard therapy is greater than a clinically meaningful difference and hence we conclude that the test drug is superior to the standard therapy.

Test for Equivalence

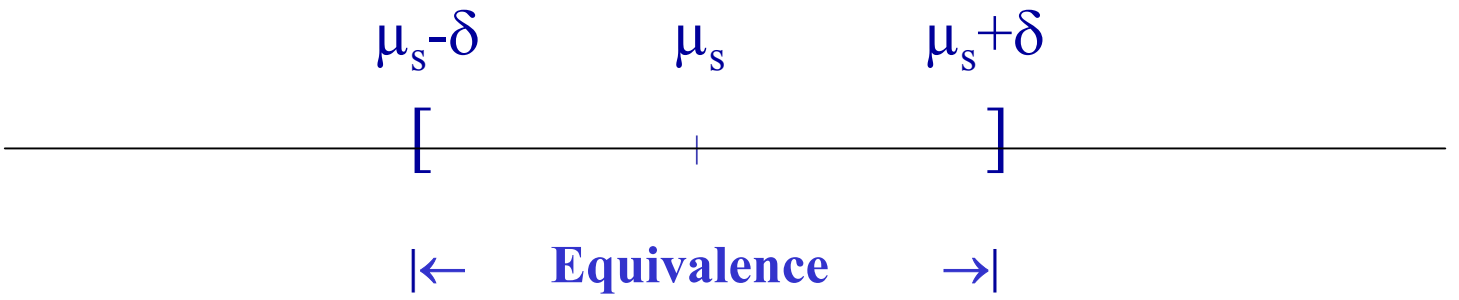
- Purpose
  - To show that the test drug can reach the same therapeutic effect as that of a standard therapy (or an active agent) or they are therapeutically equivalent
- Remark
  - It is preferred by the regulatory agency to ensure the efficacy and safety of the test drug as compare to the standard therapy

Test for Equivalence

- Hypotheses
  - Null hypothesis: There is a clinically meaningful difference between the test drug and the standard therapy
  - Alternative hypothesis: There is no clinically meaningful difference between the test drug and the standard therapy
- The rejection of the null hypothesis suggests that there is no clinically meaningful difference between the test drug and the standard therapy and hence we conclude that the test drug is superior to the standard therapy.

- Example (Hyperlipidemia)
  - μ_S
    - Standard drug, simvastatin
    - % change from baseline in LDL
  - δ (tolerated level – clinical significance level)
  - μ_T
    - Test drug, simvastatin generic
    - % change from baseline in LDL

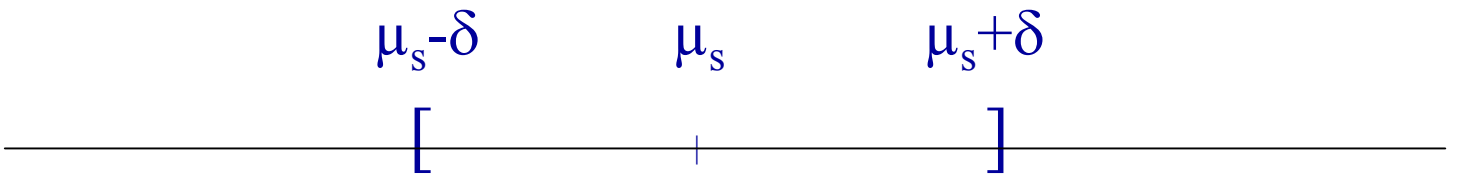
Relationship Among Non-inferiority, Superiority, and Equivalence



There is no clinically significantly meaningful difference between the test drug and the standard therapy.

It is usually referred to as two-sided equivalence.

Relationship Among Non-inferiority, Superiority, and Equivalence

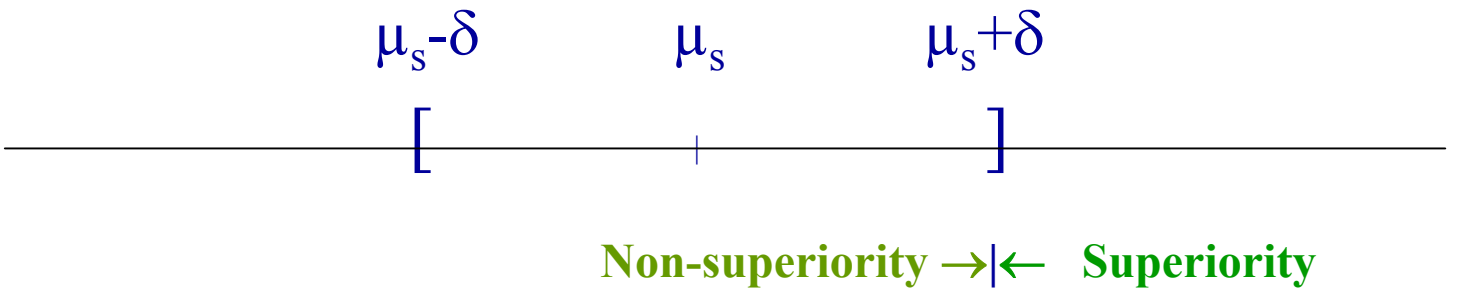


Inferiority →|← **Non-inferiority**

Non-inferiority = at least as effective as …

It is also referred to as one-sided Equivalence

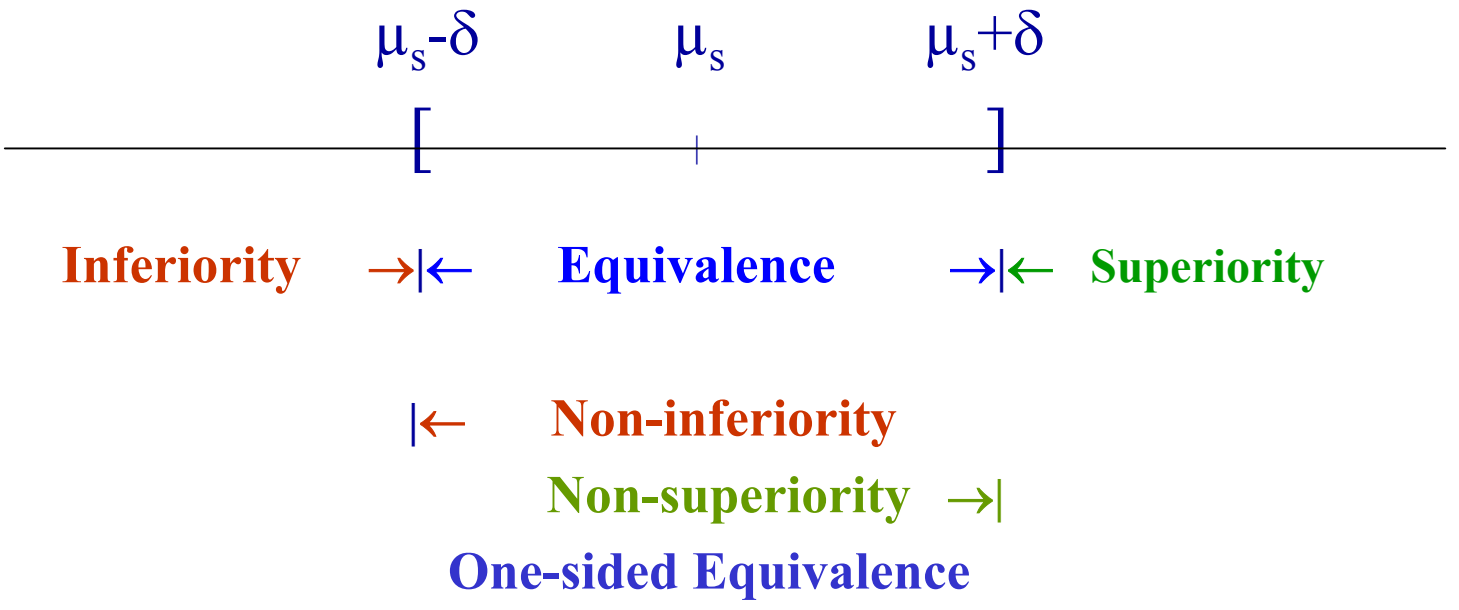
Relationship Among Non-inferiority, Superiority, and Equivalence



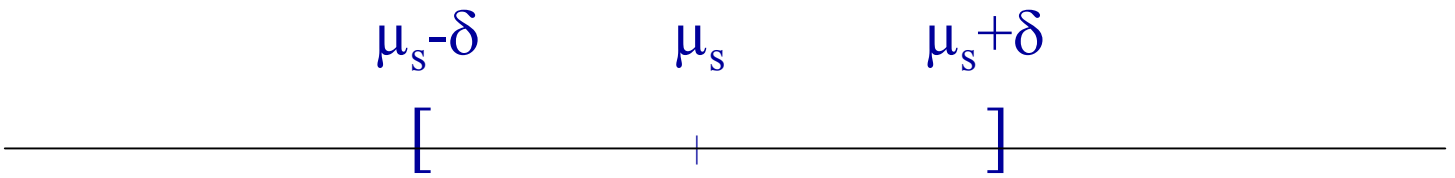
Non-superiority = at most as effective as …

It is also referred to as one-sided Equivalence

Relationship Among Non-inferiority, Superiority, and Equivalence



Relationship Among Non-inferiority, Superiority, and Equivalence



Inferiority $\rightarrow|\leftarrow$ **Equivalence** $\rightarrow|\leftarrow$ **Superiority**

Inferiority	Equivalence	Superiority
H_0: $\mu_T-\mu_s \leq -\delta$	H_0: $\lvert\mu_T-\mu_s\rvert \geq \delta$	H_0: $\mu_T-\mu_s \leq \delta$
H_a: $\mu_T-\mu_s > -\delta$	H_a: $\lvert\mu_T-\mu_s\rvert < \delta$	H_a: $\mu_T-\mu_s > \delta$

Study Designs

- Parallel design
- Crossover design
  - Standard 2x2 crossover design
  - Higher-order crossover designs
  - 2x2m replicated crossover designs
  - Williams' designs
- Multiple-stage design
  - Optimal or flexible
- Other designs

Study Designs

- Crossover vs. parallel
- Single measurement vs. repeated measurements
- Single study endpoint vs. multiple study endpoints
- With or without interim analyses
- Sample size re-estimation without unblinding

Information Required

- Study objectives
  - Test for equality
  - Test for non-inferiority/equivalence
  - Test for superiority
- Study design
  - Parallel or crossover
  - Group sequential design
  - Other designs
- Primary study endpoint(s)
  - Continuous or discrete
  - Multiple study endpoints

Information Required

- Clinically meaningful difference
  - Clinically important difference
  - Non-inferiority/superiority margin
  - Equivalence/similarity limit
- Significance level
  - 1% or 5%
- Desired power
  - 80% or 90%
- Other information, e.g.,
  - Stratification?
  - 1:1 ratio or 2:1 ratio?
  - Log-transformation?

Practical Issues

It is not uncommon to observe discrepancies

Wrong test for right hypotheses?

Right test for wrong hypotheses?

Wrong test for wrong hypotheses??

Right test for right hypotheses with insufficient power!!

Practical Issues

- Data transformation
  - Raw (untransformed) data versus log-transformed data
- Unequal assignment to treatments
  - 1:1 ratio or 2:1 ratio?
- Statistical test
  - Asymptotic versus exact
- Multiplicity
  - Closed testing procedure?

Comparing Means

Parallel Design – Equality

Hypotheses

$$H_0 : \mu_T = \mu_C \text{ vs. } H_1 : \mu_T \neq \mu_C$$

- μ_T : Population mean of the treatment
- μ_C : Population mean of the control

Parallel Design – Equality

- Test statistic $$T = \frac{\sqrt{n_T n_C}\left(\hat{\mu}_T - \hat{\mu}_C\right)}{\hat{\sigma}\sqrt{n_T + n_C}}$$
- Reject the null hypothesis if $|T| > t_{\alpha/2, n_T + n_C - 2}$
- α is the significance level
- $t_{\alpha/2, n_T + n_C - 2}$ is the $(\alpha / 2)$th upper quantile of a standard t-distribution with $n_T + n_C - 2$ degrees of freedom
- n_T and n_C are sample sizes in the treatment and the control group, respectively.

Parallel Design – Equality

Power

$$1-\beta = P\left(\left|\mathrm{T}\right| > \mathrm{t}_{\alpha/2,\, n_\mathrm{T}+n_\mathrm{C}-2}\right)$$

$$\approx \Phi\left(\frac{\sqrt{n_\mathrm{T} n_\mathrm{C}}\left|\mu_\mathrm{T}-\mu_\mathrm{C}\right|}{\sigma\sqrt{n_\mathrm{T}+n_\mathrm{C}}} - z_{\alpha/2}\right)$$

- σ: standard deviation
- β: the probability of committing a type II error
- $z_{\alpha/2}$: the $(\alpha/2)$th upper quantile of a standard normal distribution

Parallel Design – Equality

Sample size calculation

$$n_T = k n_C \text{ and } n_C = \frac{(z_{\alpha/2} + z_\beta)^2 \sigma^2 (1 + 1/k)}{(\mu_T - \mu_C)^2}$$

- k : sample size allocation (treatment/control)

Parallel Design – Equality

Sample size calculation

k=1 (i.e., 1:1 ratio)

$$n_C = \frac{2 \times (z_{\alpha/2} + z_\beta)^2 \sigma^2}{(\mu_T - \mu_C)^2}$$

k=2 (i.e., 2:1 ratio)

$$n_C = \frac{1.5 \times (z_{\alpha/2} + z_\beta)^2 \sigma^2}{(\mu_T - \mu_C)^2}$$

Parallel Design – Equality

Example

- Objective: Comparing Treatment with Control in terms of improving bone density in patients with osteoporosis
- Design: A two-arm parallel-group design
- Primary study endpoint: bone density
- Clinically meaningful difference: 0.05
- Standard deviation: 0.10
- Type I and II error: 5% and 20%, respectively
- Sample size allocation: 1:1

Parallel Design – Equality

Example

$$n_T = n_C = \frac{(1.96+0.84)^2 0.10^2 (1+1/1)}{0.05^2}$$

$$= 62.72 \approx 63$$

- As a result, a total of 126 subjects (63 per treatment group) are needed for achieving an 80% power for detection of a clinically meaningful difference.

Parallel Design – Non-Inferiority/Superiority

Hypotheses

$$H_0 : \mu_T - \mu_C < \delta \text{ vs. } H_1 : \mu_T - \mu_C \geq \delta$$

- μ_T: Population mean of the treatment
- μ_C: Population mean of the control
- δ: Non-inferiority (if less than 0) or superiority (if greater than 0) margin.

Parallel Design – Non-Inferiority/Superiority

- Test statistic

$$T = \frac{\sqrt{n_T n_C}\left(\hat{\mu}_T - \hat{\mu}_C - \delta\right)}{\hat{\sigma}\sqrt{n_T + n_C}}$$

- Reject the null hypothesis if $T > t_{\alpha, n_T + n_C - 2}$

Parallel Design – Non-Inferiority/Superiority

Power

$$1-\beta = \mathrm{P}\left(\mathrm{T} > \mathrm{t}_{\alpha,\mathrm{n_T}+\mathrm{n_C}-2}\right)$$

$$= \Phi\left(\frac{\sqrt{n_\mathrm{T} n_\mathrm{C}}\left(\mu_\mathrm{T}-\mu_\mathrm{C}-\delta\right)}{\sigma\sqrt{n_\mathrm{T}+n_\mathrm{C}}} - z_\alpha\right)$$

Parallel Design – Non-Inferiority/Superiority

Sample size calculation

$$n_T = k n_C \text{ and } n_C = \frac{(z_\alpha + z_\beta)^2 \sigma^2 (1 + 1/k)}{(\mu_T - \mu_C - \delta)^2}$$

- k: sample size allocation (treatment/control)

Parallel Design – Non-Inferiority/Superiority

Sample size calculation

$$n_C = \frac{2\times(z_\alpha + z_\beta)^2\sigma^2}{(\mu_T - \mu_C - \delta)^2} \quad \text{if k=1}$$

$$n_C = \frac{1.5\times(z_\alpha + z_\beta)^2\sigma^2}{(\mu_T - \mu_C - \delta)^2} \quad \text{if k=2}$$

Parallel Design – Non-Inferiority/Superiority

Example

- Primary study endpoint: bone density
- Design: A two-arm parallel design
- True difference: 0%
- Non-inferiority margin: -0.05
- Standard deviation: 0.10
- Type I and II error: 5% and 20%, respectively
- Sample size allocation: 1:1

Parallel Design – Non-Inferiority/Superiority

Example

$$n_T = n_C = \frac{(1.64+0.84)^2 0.10^2 (1+1/1)}{(0-(-0.05))^2}$$

$$= 49.20 \approx 50$$

- As a result, a total of 100 subjects (50 per treatment group) are needed for achieving an 80% power for demonstration of non-inferiority.

Parallel Design – Equivalence

Hypotheses

$$H_0 : |\mu_T - \mu_C| \geq \delta \text{ vs. } H_1 : |\mu_T - \mu_C| < \delta$$

- μ_T: Population mean of the treatment
- μ_C: Population mean of the control
- δ: Equivalence limit.

Parallel Design – Equivalence

Two one-sided test procedure (Schuirmann, 1987)

- Test statistics

$$T_1 = \frac{\sqrt{n_T n_C}\left(\hat{\mu}_T - \hat{\mu}_C - \delta\right)}{\hat{\sigma}\sqrt{n_T + n_C}}$$

$$T_2 = \frac{\sqrt{n_T n_C}\left(\hat{\mu}_T - \hat{\mu}_C + \delta\right)}{\hat{\sigma}\sqrt{n_T + n_C}}$$

- Reject the null hypothesis if

$$T_1 < -t_{\alpha, n_T + n_C - 2} \text{ and } T_2 > t_{\alpha, n_T + n_C - 2}$$

Parallel Design – Equivalence

Power

$$1-\beta = \Phi\left(\frac{\sqrt{n_T n_C}\left(\delta - \left|\mu_T - \mu_C\right|\right)}{\sigma\sqrt{n_T + n_C}} - z_\alpha\right) + \Phi\left(\frac{\sqrt{n_T n_C}\left(\delta + \left|\mu_T - \mu_C\right|\right)}{\sigma\sqrt{n_T + n_C}} - z_\alpha\right) - 1$$

Parallel Design – Equivalence

Sample size calculation

$$n_C = \begin{cases} \dfrac{(z_\alpha + z_{\beta/2})^2 \sigma^2 (1+1/k)}{\delta^2} & \text{if } \mu_T = \mu_C \\ \dfrac{(z_\alpha + z_\beta)^2 \sigma^2 (1+1/k)}{(\delta - |\mu_T - \mu_C|)^2} & \text{if } \mu_T \neq \mu_C \end{cases}$$

where $n_T = k n_C$

Parallel Design – Equivalence

Sample size calculation with 1:1 ration (i.e., k=1)

$$n_C = \begin{cases} \dfrac{2\times(z_\alpha + z_{\beta/2})^2\sigma^2}{\delta^2} & \text{if } \mu_T = \mu_C \\ \dfrac{2\times(z_\alpha + z_\beta)^2\sigma^2}{(\delta - |\mu_T - \mu_C|)^2} & \text{if } \mu_T \neq \mu_C \end{cases}$$

Parallel Design – Equivalence

Sample size calculation with 2:1 ratio (i.e., k=2)

$$n_C = \begin{cases} \dfrac{1.5\times(z_\alpha + z_{\beta/2})^2\sigma^2}{\delta^2} & \text{if } \mu_T = \mu_C \\ \dfrac{1.5\times(z_\alpha + z_\beta)^2\sigma^2}{(\delta - |\mu_T - \mu_C|)^2} & \text{if } \mu_T \neq \mu_C \end{cases}$$

Parallel Design – Equivalence

Example

- Primary study endpoint: bone density
- Design: A two-arm parallel design
- True difference: 0.05
- Equivalence limit: 0.15
- Standard deviation: 0.10
- Type I and II error: 5% and 20%, respectively
- Sample size allocation: 1:1

Parallel Design – Equivalence

Example

$$n_C = \frac{2 \times (1.64 + 0.84)^2 \times 0.10^2}{(0.15 - |0.05|)^2}$$

$$= 12.3 \approx 13$$

- As a result, a total of 26 subjects (13 per treatment group) are needed in order to achieve for establishment of equivalence.

Comparing Means

- 處方：C口服液
- 適應症：骨質疏鬆症
- 臨床試驗目的：骨密度(BMD)增加
- 試驗設計：Active Control
  - 實驗組： C口服液
  - 對照組： C 錠劑
- 主要評估指標：服用藥物一年後骨密度變化百分比

Comparing Means

- 試驗假說：

$$H_0 : |\mu_T - \mu_C| \geq \delta \text{ vs. } H_1 : |\mu_T - \mu_C| < \delta$$

- 樣本數推估
  - 指標參數：骨密度變化百分比
  - 顯著水準：0.05
  - 檢定力：80%
  - Equivalence Limit δ : 1.5%
  - 評估所需樣本數：140
    - 實驗組：70
    - 對照組：70

Comparing Proportions

Parallel Design - Asymptotic

Hypotheses for testing equality

$$\mathrm{H}_0 : p_\mathrm{T} = p_\mathrm{C} \text{ vs. } \mathrm{H}_1 : p_\mathrm{T} \neq p_\mathrm{C}$$

- p_T : true proportion of the treatment
- p_C : true proportion of the control

Parallel Design - Asymptotic

- Test statistic

$$Z = \frac{\hat{p}_T - \hat{p}_C}{\sqrt{\hat{p}_T(1-\hat{p}_T)/n_T + \hat{p}_C(1-\hat{p}_C)/n_C}}$$

- Reject the null hypothesis if $|Z| > z_{\alpha/2}$
- α is the significant level
- $z_{\alpha/2}$ is the $(\alpha/2)$th upper quantile of a standard normal distribution
- n_T and n_C : sample size in the treatment and the control group, respectively.

Parallel Design - Asymptotic

Power

$$1-\beta=\Phi\left(\frac{\left|p_{\mathrm{T}}-p_{\mathrm{C}}\right|}{\sqrt{p_{\mathrm{T}}(1-p_{\mathrm{T}})/n_{\mathrm{T}}+p_{\mathrm{C}}(1-p_{\mathrm{C}})/n_{\mathrm{C}}}}-z_{\alpha/2}\right)$$

- β : type II error

Parallel Design - Asymptotic

Sample size calculation

$$\begin{cases} n_{\mathrm{T}} = k n_{\mathrm{C}} \\ n_{\mathrm{C}} = \dfrac{(z_{\alpha/2} + z_{\beta})^2}{(p_{\mathrm{T}} - p_{\mathrm{C}})^2} \left[p_{\mathrm{T}}(1 - p_{\mathrm{T}})/k + p_{\mathrm{C}}(1 - p_{\mathrm{C}}) \right] \end{cases}$$

- k: sample size allocation (treatment/control)

Parallel Design - Asymptotic

Sample size calculation

$$n_C = \frac{(z_{\alpha/2} + z_\beta)^2}{(p_T - p_C)^2}\left[p_T(1-p_T) + p_C(1-p_C)\right] \text{ if } k = 1$$

$$n_C = \frac{(z_{\alpha/2} + z_\beta)^2}{(p_T - p_C)^2}\left[p_T(1-p_T)/2 + p_C(1-p_C)\right] \text{ if } k = 2$$

Parallel Design - Asymptotic

Example

- Objective
  - To compare the relapse rate of patients in a cancer trial comparing a test treatment with a control
- Design
  - A two-arm parallel-group design
- True proportion for patients in the control group: 10%
- Clinically significant improvement: 5%
- Type I and II errors are 5% and 20%, respectively
- Treatment allocation: 1:1 ratio

Parallel Design - Asymptotic

Example

$$n_C = \frac{(1.96+0.84)^2}{(0.10-0.05)^2}\left[0.10(1-0.10)+0.05(1-0.05)\right]$$

$$= 431.20 \approx 432$$

- As a result, a total of 864 subjects (432 per treatment group) are needed in order to achieve an 80% power for detection of a 5% difference in relapse rate.

Comparing Proportions

- 處方：萬能湯加減方
- 適應症：要命的病
- 臨床試驗目的：功能性指標（functional outcome）改善狀況
- 試驗設計：Add-On
  - 實驗組：Drug A + 試驗藥物
  - 對照組：Drug A

Comparing Proportions

- 主要評估指標：經4週藥物治療及8週追蹤期後之有效率
  - 有效率須滿足下列全部條件：
    - Alive
    - A Scale < 3
    - B Index (BI) ≥ 60

Comparing Proportions

試驗假說：

$$H_0 : p_T = p_C \text{ vs. } H_1 : p_T \neq p_C$$

- 樣本數推估
  - 指標參數：有效率
  - 顯著水準：0.05（雙尾檢定）
  - 檢定力：80%
  - 評估所需樣本數：300
    - 實驗組：150
    - 對照組：150

Two Stage Design in Cancer Trials

- Objective
  - Test Therapy: New Combination Therapy
  - Indication: Advance Gastric Cancer
  - Target response rate: 30%
  - Standard response rate: 15%
  - Hypotheses

$$H_0: p \leq 0.15$$

vs. Ha: $p \geq 0.30$

Two Stage Design in Cancer Trials

- α =5%
- β =20%
- Two-stage optimal design

  (Richard Simon, 1989) gives

$(r_1/n_1, r_2/n_2) = (3/19, 12/55)$

Two Stage Design in Cancer Trials

- Stage 1
  - 19 patients are to be treated.
  - Terminates the trial of no more than 3 response are observed.
  - If there are 4 or more responses, then continues.
- Stage 2
  - Additional 36 patients are tested.
  - Conclude that test drug is effective (has achieved the desired response rate) if there are more than 12 responses in the 55 patients

Comparing Time-to-event Data

Parallel Design – Non-Inferiority/Superiority

Hypotheses

$$H_0 : \lambda_C - \lambda_T < \delta \text{ vs. } H_1 : \lambda_C - \lambda_T \geq \delta$$

- λ_T: Hazard rate of the treatment
- λ_C: Hazard rate of the control
- δ: Non-inferiority (if less than 0) or superiority (if greater than 0) margin.

Parallel Design – Non-Inferiority/Superiority

- Test statistic

$$T = \frac{\hat{\lambda}_C - \hat{\lambda}_T - \delta}{\sqrt{\sigma^2(\hat{\lambda}_C)/n_C + \sigma^2(\hat{\lambda}_T)/n_T}}$$

- Reject the null hypothesis if $T > z_\alpha$

Parallel Design – Non-Inferiority/Superiority

Power

$$1-\beta=\Phi\left(\frac{\lambda_C-\lambda_T-\delta}{\sqrt{\sigma^2(\lambda_C)/n_C+\sigma^2(\lambda_T)/n_T}}-z_\alpha\right)$$

Parallel Design – Non-Inferiority/Superiority

Sample size calculation

$$n_T = k n_C \text{ and } n_C = \frac{(z_\alpha + z_\beta)^2}{(\lambda_C - \lambda_T - \delta)^2}\left[\sigma^2(\lambda_C) + \sigma^2(\lambda_T)/k\right]$$

- k: sample size allocation (treatment/control)

Parallel Design – Non-Inferiority/Superiority

Sample size calculation

$$n_C = \frac{(z_\alpha + z_\beta)^2}{(\lambda_C - \lambda_T - \delta)^2}\left[\sigma^2(\lambda_C) + \sigma^2(\lambda_T)\right] \text{ if } k = 1$$

$$n_C = \frac{(z_\alpha + z_\beta)^2}{(\lambda_C - \lambda_T - \delta)^2}\left[\sigma^2(\lambda_C) + \sigma^2(\lambda_T)/2\right] \text{ if } k = 2$$

Parallel Design – Non-Inferiority/Superiority

Example

- Design
  - A two-arm parallel-group design
- Assumptions
  - 1 year accrual plus 2 years follow-up
  - Primary study endpoint: time-to-relapse
  - Hazard rate under Treatment: 1
  - Hazard rate under Reference: 2
  - Superiority margin: 0.2
  - Type I and II error: 5% and 20%, respectively
- Sample size allocation: 1:1

Parallel Design – Non-Inferiority/Superiority

Example

$$n_T = n_C = \frac{(1.64+0.84)^2}{(2-1-0.2)^2}(0.97+3.94)$$

$$\approx 48$$

- As a result, a total of 96 subjects (48 per treatment group) are needed for achieving an 80% power for demonstration of non-inferiority.

Genomics

- Matched-pairs design
- Completely randomized design
- Isolated-effect design

- Lee, M.-L., Whitmore, G.A. (2002) *Power and sample size for DNA microarray studies.* Stat. Med. 21:3543-3570.

Summary

- Comparing Means
- Comparing Proportions
- Comparing Time-to-event Data

Comparing Means - Parallel Design

Summarization

$$\text{Equal} \quad : n_C = \frac{(z_{\alpha/2} + z_\beta)^2 \sigma^2 (1 + 1/k)}{(\mu_T - \mu_C)^2}$$

$$\text{NI/SU} \quad : n_C = \frac{(z_\alpha + z_\beta)^2 \sigma^2 (1 + 1/k)}{(\mu_T - \mu_C - \delta)^2}$$

$$\text{Equi} \quad : n_C = \frac{(z_\alpha + z_{\beta/2})^2 \sigma^2 (1 + 1/k)}{\delta^2} \quad \text{if} \quad \mu_T = \mu_C$$

$$\text{Equi} \quad : n_C = \frac{(z_\alpha + z_\beta)^2 \sigma^2 (1 + 1/k)}{\left(\delta - |\mu_T - \mu_C|\right)^2} \quad \text{if} \quad \mu_T \neq \mu_C$$

*: Equal – equality; NI/SU – non-inferiority/superiority; Equiv: equivalence.

Comparing Means - Crossover Design

Summarization

$$\text{Equal} \quad : n = \frac{(z_{\alpha/2} + z_{\beta})^2 \sigma^2}{2(\mu_T - \mu_C)^2}$$

$$\text{NI/SU} \quad : n = \frac{(z_{\alpha} + z_{\beta})^2 \sigma^2}{2(\mu_T - \mu_C - \delta)^2}$$

$$\text{Equi} \quad : n = \frac{(z_{\alpha} + z_{\beta/2})^2 \sigma^2}{2\delta^2} \quad \text{if} \quad \mu_T = \mu_C$$

$$\text{Equi} \quad : n = \frac{(z_{\alpha} + z_{\beta})^2 \sigma^2}{2\left(\delta - |\mu_T - \mu_C|\right)^2} \quad \text{if} \quad \mu_T \neq \mu_C$$

*: Equal – equality; NI/SU – non-inferiority/superiority; Equiv: equivalence.

Comparing Proportions - Parallel Design (Asymptotic)

Summarization

$$\text{Equal}: n_C = \frac{(z_{\alpha/2} + z_\beta)^2}{(p_T - p_C)^2}\left(p_T(1-p_T)/k + p_C(1-p_C)\right)$$

$$\text{NI/SU}: n_C = \frac{(z_{\alpha} + z_\beta)^2}{(p_T - p_C - \delta)^2}\left(p_T(1-p_T)/k + p_C(1-p_C)\right)$$

$$\text{Equi}: n_C = \frac{(z_{\alpha} + z_{\beta/2})^2}{\delta^2}\left(p_T(1-p_T)/k + p_C(1-p_C)\right) \text{ if } \mu_T = \mu_C$$

$$\text{Equi}: n_C = \frac{(z_{\alpha} + z_{\beta})^2}{\left(\delta - |p_T - p_C|\right)^2}\left(p_T(1-p_T)/k + p_C(1-p_C)\right) \text{ if } \mu_T \neq \mu_C$$

*: Equal – equality; NI/SU – non-inferiority/superiority; Equiv: equivalence.

Comparing Time-to-event Parallel Design

Summarization

$$\text{Equal} \quad : n_C = \frac{(z_{\alpha/2} + z_\beta)^2}{(\lambda_C - \lambda_T)^2}\left[\sigma^2(\lambda_C) + \sigma^2(\lambda_T)/k\right]$$

$$\text{NI/SU} \quad : n_C = \frac{(z_{\alpha} + z_\beta)^2}{(\lambda_C - \lambda_T - \delta)^2}\left[\sigma^2(\lambda_R) + \sigma^2(\lambda_T)/k\right]$$

$$\text{Equi} \quad : n_C = \frac{(z_{\alpha} + z_{\beta/2})^2}{\delta^2}\left[\sigma^2(\lambda_R) + \sigma^2(\lambda_T)/k\right] \text{ if } \mu_T = \mu_C$$

$$\text{Equi} \quad : n_C = \frac{(z_{\alpha} + z_\beta)^2}{\left(\delta - |\lambda_C - \lambda_T|\right)^2}\left[\sigma^2(\lambda_R) + \sigma^2(\lambda_T)/k\right] \text{ if } \mu_T \neq \mu_C$$

*: Equal – equality; NI/SU – non-inferiority/superiority; Equiv: equivalence.