ST520 Statistical Principles of Clinical Trials

1 Introduction

1.1 Brief Introduction to Epidemiology

- **Prevalence** of disease $P(D)$
- **Incidence** of disease: probability of getting disease during a certain time period
- **Relative risk** $\psi = \frac{P(D|E)}{P(D|\overline{E})}$ (easier interpretation, association not causation)
- **Odds ratio** $\theta = \frac{P(D|E)/\{1-P(D|E)\}}{P(D|\overline{E})/\{1-P(D|\overline{E})\}}$
- $\psi > 1 (= 1, < 1) \Longleftrightarrow \theta > 1 (= 1, < 1)$
- For rare disease, $P(D \mid E) \approx 0$ and $P(D \mid \overline{E}) \approx 0$, then $\theta \approx \psi$
- Estimates
  - $\hat{\theta} = \frac{n_{11}n_{22}}{n_{12}n_{21}}$
  - $\hat{V}\{\log(\hat{\theta})\} = \frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}$
  - $\hat{V}(\hat{\theta}) = \hat{\theta}^2 \left(\frac{1}{n_{11}} + \frac{1}{n_{12}} + \frac{1}{n_{21}} + \frac{1}{n_{22}}\right)$

Cross-sectional study

- can estimate $P(D)$, $P(D \mid E)$ and the similar type (i.e., $P(\bar{D})$, $P(D \mid \bar{E})$, and so on), ψ, θ

Longitudinal study

- Prospective
  - can estimate $P(D \mid E)$ and the similar type, ψ, θ
- Retrospective: case-control
  - can estimate $P(E \mid D)$ and the similar type, θ (ψ for rare disease)

1.2 Brief Introduction and History of Clinical Trials

2 Phase I and II clinical trials

2.1 Phases of Clinical Trials

- Phase I (toxicity and dose-finding)
- Phase II (screening and feasibility)
- Phase III (comparative study)
- Phase IV (post marketing)

2.2 Phase II clinical trials

- surrogate markers
- Example (a binary endpoint): π =the response rate
  - X =the number of responses among a random sample of n
  - $X \sim b(n, \pi)$
  - Normal approximation $p = X/n \sim N\left(\pi, \frac{\pi(1-\pi)}{n}\right)$
  - $(1-\alpha)$ confidence interval $p \pm z_{1-\alpha/2}\left\{\frac{p(1-p)}{n}\right\}^{1/2}$
- Exact confidence interval $C(X)$ such that $C(k) = (\pi_L(k), \pi_U(k))$
  - $P_{\pi_L(k)}(X \geq k) = \sum_{j=k}^{n} \left(\begin{array}{c} n \\ j \end{array} \right) \pi_L(k)^j \{1-\pi_L(k)\}^{n-j} = \alpha/2$
  - $P_{\pi_U(k)}(X \leq k) = \sum_{j=0}^{k} \left(\begin{array}{c} n \\ j \end{array} \right) \pi_U(k)^j \{1-\pi_U(k)\}^{n-j} = \alpha/2$
- **Gehan**'s two-stage design
  - Stage I. (start with n_0 and a minimum acceptable response rate π_0) if no one responds, declare a failure.
    - determine $n_0 : P_\pi(X=0) \leq (1-\pi_0)^{n_0} \leq \alpha$
  - Stage II. (add $n - n_0$) count the total number of responses, calculate p and construct a CI for π.

  - $*$ determine n : based on the precision of 95% CI using π_0.

- The expected sample size is

$$\begin{aligned} & n_0 P(\text{stopping at Stage I}) + nP(\text{stopping at Stage II}) \\ = \quad & n_0 P(X = 0 \mid \pi_0) + n\{1 - P(X = 0 \mid \pi_0)\} = (n_0 - n)(1 - \pi_0)^{n_0} + n \end{aligned}$$

- **Simon**'s two-stage design (n_1, n, r_1, r) with $\pi_0 < \pi_1$

  - Stage I. (start with n_1) $X_1 \sim b(n_1, \pi)$ if $X_1 \leq r_1$, declare a failure.
  - Stage II. (add $n_2 = n - n_1$) $X_2 \sim b(n_2, \pi)$ if $X_1 + X_2 \leq r$, declare a failure.

    constraints:

    - $*$ $P(\text{success} \mid \pi \leq \pi_0) \leq \alpha \Leftrightarrow P\{(X_1 > r_1)\&(X_1 + X_2 > r) \mid \pi = \pi_0\} \leq \alpha$
    - $*$ $P(\text{failure} \mid \pi \geq \pi_1) \leq \beta \Leftrightarrow P\{(X_1 > r_1)\&(X_1 + X_2 > r) \mid \pi = \pi_1\} \geq 1 - \beta$
  - Optimal design : to minimize the expected sample size

$$\begin{aligned} & n_1 P(\text{stopping at Stage I}) + nP(\text{stopping at Stage II}) \\ = \quad & n_1 P(X_1 \leq r_1 \text{or } X_1 > r \mid \pi_0) + nP(r_1 + 1 \leq X_1 \leq r \mid \pi_0). \end{aligned}$$

3 Phase III clinical trials

3.1 Why are clinical trials needed

3.2 Issues to consider before designing a clinical trial

3.3 Ethical issues

3.4 The randomized clinical trial - hierarchical models

- To address the question of whether the results from the different studies are random samples form underlying groups with a common response rate or from groups with different underlying response rates.
- Hierarchical models for (n_i, X_i, π_i) $i = 1, \ldots, N$
  - (1st) $\pi_1, \ldots, \pi_N \overset{iid}{\sim} (\mu_\pi, \sigma^2_\pi)$
  - (2rd) $X_i \mid n_i, \pi_i \sim b(n_i, \pi_i), i = 1, \ldots, N$
- Goal is to estimate σ^2_π
- **Law of conditional expectation**: $E(X) = E\{E(X \mid Y)\}$
- **Law of conditional variance**: $V(X) = E\{V(X \mid Y)\} + V\{E(X \mid Y)\}$
- $p_i = X_i/n_i$
  - $E(p_i \mid \pi_i, n_i) = \pi_i$
  - $V(p_i \mid \pi_i, n_i) = \pi_i(1 - \pi_i)/n_i$
  - $E(p_i) = E\{E(p_i \mid \pi_i, n_i)\} = \mu_\pi$
  - $V(p_i) = E\{V(p_i \mid \pi_i, n_i)\} + V\{E(p_i \mid \pi_i, n_i)\} = E\{\pi_i(1 - \pi_i)/n_i\} + \sigma^2_\pi$
- $\bar{p} = N^{-1} \sum_{i=1}^N p_i$
- $s^2_p = \frac{\sum_{i=1}^N (p_i - \bar{p})^2}{N-1}$: $E(s^2_p) = V(p_i)$
- $N^{-1} \sum_{i=1}^N \frac{p_i(1-p_i)}{n_i - 1}$: $E\left\{N^{-1} \sum_{i=1}^N \frac{p_i(1-p_i)}{n_i-1}\right\} = E\left\{\frac{\pi_i(1-\pi_i)}{n_i}\right\}$
- $\hat{\sigma}^2_\pi = \left\{\frac{\sum_{i=1}^N (p_i - \bar{p})^2}{N-1}\right\} - \left\{N^{-1} \sum_{i=1}^N \frac{p_i(1-p_i)}{n_i-1}\right\}$ is unbiased for σ^2_π.

- $\hat{\mu}_\pi = \frac{p_1 + ... + p_N}{N}$

4 Randomization

- Advantage of randomization: eliminate conscious and unconscious biases
- Disadvantage of randomization:
  - interference with physician patient relationship
  - resources expended in the control group

4.1 Inference

4.1.1 Design-based inference

- Sharp null hypothesis: A & B (two treatments) are exactly the same for each patient
- Test statistics: T =difference of the sample means
- The distribution of test statistics is induced by the randomization $\implies$ the permutation distribution of T
- One-sided p-value (the alternative is "A is better than B") $P(T \geq t_{obs} \mid \text{sharp } H_0) = \frac{\#\text{of } t_i \geq t_{obs}}{\#\text{of } t_i \text{ under permutation}}$
- Two-sided p-value (the alternative is "A is different than B") $P(|T| \geq |t_{obs}| \mid \text{sharp } H_0) = \frac{\#\text{of } |t_i| \geq |t_{obs}|}{\#\text{of } t_i}$
- Remark: In the permutational distribution, we treat each individual's response as fixed. Randomness is induced by the treatment assignment mechanism.

4.1.2 Model-based inference

- The distribution of test statistics is induced by assumptions about a super-population and a probability model.
- Statistical model:
- $Y_1, Y_2 \overset{iid}{\sim} N(\mu_A, \sigma^2)$
- $Y_3, Y_4 \overset{iid}{\sim} N(\mu_B, \sigma^2)$
- Null hypothesis: $H_0 : \mu_A = \mu_B$

- $T = \frac{\bar{Y}_A - \bar{Y}_B}{s_p(n_A^{-1}+n_B^{-1})^{1/2}} \overset{H_0}{\sim} t_{n_A+n_B-2}$
- p-value= $P(t_{n_A+n_B-2} \geq t_{obs} \mid H_0)$

4.1.3 Causal inference from an experimental sample to a larger population

- Potential outcomes $Y^*(1)$ and $Y^*(2)$
- The average treatment effect is ATE= $E\{Y^*(2) - Y^*(1)\}$
- Treatment indicator $A \in \{1, 2\}$
- Observed outcome $Y = Y^*(1)I(A = 1) + Y^*(2)I(A = 2) = Y^*(A)$ under SUTVA
- Randomization: $A \perp\!\!\!\perp \{Y^*(1), Y^*(2)\}$
  - implication $E\{Y^*(a)\} = E\{Y^*(a) \mid A = a\} = E\{Y \mid A = a\} \equiv \mu_a$ for $a = 1, 2$
  - $\mu_2 - \mu_1$ is the same as ATE
  - estimator: $\bar{Y}_2 - \bar{Y}_1$

4.2 Fixed allocation randomization

1. Simple randomization
   - Two treatments A & B; $\Delta = \mu_2 - \mu_1$; $\hat{\Delta} = \bar{Y}_2 - \bar{Y}_1$
   - Treatment allocation with $P(A) = \pi$
   - $V(\hat{\Delta}) = \sigma^2 \left(\frac{1}{n_1} + \frac{1}{n_2}\right)$
   - Advantage: easy; impossible to guess the next treatment assignment; iid
   - Disadvantage: possibility of severe treatment imbalance
2. Permuted block randomization
   - try to balance A & B
   - fixed block size
   - varying block size

3. Stratified randomization (permuted block randomization): see homework 3 additional question

   - The maximum imbalance between A & B is # of strata$\times$(block size)/2
   - Advantage: treatment groups are similar; more precise estimates of treatment difference
   - Disadvantage: too many prognostic factors to form strata, very few (or even zero) patient in some strata, back to simple randomization

- Linear combination of random variables
  - Let $Z_1, \ldots, Z_m$ be random variables, and let $a_0, \ldots, a_m$ be constants
  - $E(a_0 + a_1 Z_1 + \ldots + a_m Z_m) = a_0 + a_1 E(Z_1) + \ldots + a_m E(Z_m)$
  - In addition, $Z_1, \ldots, Z_m$ are mutually independent, then $V(a_0 + a_1 Z_1 + \ldots + a_m Z_m) = a_1^2 V(Z_1) + \ldots + a_m^2 V(Z_m)$
  - Eg. Let $X_1, \ldots, X_n \overset{iid}{\sim}$ be random variables, and let $a_0, \ldots, a_m$ be constants
  - $E(a_0 + a_1 Z_1 + \ldots + a_m Z_m) = a_0 + a_1 E(Z_1) + \ldots + a_m E(Z_m)$
  - In addition, $Z_1, \ldots, Z_m$ are mutually independent, then $V(a_0 + a_1 Z_1 + \ldots + a_m Z_m) = a_1^2 V(Z_1) + \ldots + a_m^2 V(Z_m)$

- Effect of blocking within strata on the precision of estimators
  - $Y_i = \mu + \alpha S_i + \beta X_i + \epsilon_i$, strata indicator $S_i \in \{0, 1\}$, treatment indicator $X_i \in \{0, 1\}$,$\epsilon_i \overset{iid}{\sim} (0, \sigma^2)$
  - $\hat{\Delta} = \bar{Y}_A - \bar{Y}_B$
  - Under stratified randomization: $V(\hat{\Delta}) = \frac{4\sigma^2}{n}$
  - Under permuted block randomization: $V(\hat{\Delta}) = \sigma^2 \frac{4}{n}$
  - Under simple randomization: $V(\hat{\Delta}) = \{\sigma^2 + \alpha^2 \theta(1-\theta)\} E\left(\frac{1}{n_A} + \frac{1}{n - n_A}\right)$
  - The test statistics $T = \frac{\bar{Y}_A - \bar{Y}_B}{s_p(\frac{1}{n_A} + \frac{1}{n_B})^{1/2}}$ is conservative in a stratified random design with $\alpha \neq 0$ (i.e. some strata effect)

4.3 Baseline adaptive randomization

- Efron biased coin design

- Urn Model (L.J. Wei)
- Minimization method of Pocock and Simon

4.4 Response adaptive randomization

- Play-the-Winner Rule (Zelen)
- Urn Model (L.J. Wei)

5 Some additional issues in Phase III clinical trails

- Blinding and Placebos
- Ethics
- The protocol document

6 Sample Size Calculations

- Generally, $\begin{cases} T_n \overset{\Delta=0}{\sim} N(0,1) & \Rightarrow \text{one-sided level-}\alpha \text{ test} \Rightarrow \text{rejection region: } T_n \geq z_\alpha \\ T_n \overset{\Delta=\Delta_A}{\sim} N(\phi(n,\Delta_A,\theta), \sigma_*^2(\Delta_A,\theta)) & \Rightarrow \text{power: } P_{\Delta=\Delta_A}(T_n \geq z_\alpha) = 1-\beta \end{cases}$
- Key formula for sample size calculation:

$$\phi(n,\Delta_A,\theta) = \begin{cases} Z_\alpha + Z_\beta \sigma_*(\Delta_A,\theta) \text{ for a one-sided test} \\ Z_{\alpha/2} + Z_\beta \sigma_*(\Delta_A,\theta) \text{ for a two-sided test} \end{cases}$$

6.1 Comparison of two means

- $H_0 : \Delta = \mu_1 - \mu_2 \leq 0$ vs $H_A : \Delta > 0$
- $Y_i \mid A_i = 1 \sim (\mu_1, \sigma^2)$, $Y_i \mid A_i = 2 \sim (\mu_2, \sigma^2)$
- $T_n = \dfrac{\bar{Y}_1 - \bar{Y}_2}{s_p \sqrt{\frac{1}{n_1} + \frac{1}{n_2}}}$
- $\begin{cases} T_n \overset{\Delta=0}{\sim} N(0,1) \\ T_n \overset{\Delta=\Delta_A}{\sim} N\left(\dfrac{\Delta_A}{\sigma\sqrt{\frac{1}{n_1}+\frac{1}{n_2}}}, 1 \right) \end{cases}$

6.2 Comparison of two proportions

- Hypothesis testing: $H_0 : \pi_1 \leq \pi_2$ ($\Delta = \pi_1 - \pi_2 \leq 0$) vs $H_A : \pi_1 > \pi_2 (\Delta > 0)$
- Data: $X_1 \sim b(n_1, \pi_1)$, $X_2 \sim b(n_2, \pi_2)$, $p_1 = \frac{X_1}{n_1}$ and $p_2 = \frac{X_2}{n_2}$ ($n_1 = n_2 = \frac{n}{2}$)
- $T_1 = \dfrac{p_1 - p_2}{\sqrt{\bar{p}(1-\bar{p})(\frac{1}{n_1}+\frac{1}{n_2})}}, \bar{p} = \frac{X_1+X_2}{n_1+n_2}$
- $\begin{cases} T_1 \overset{\Delta=0}{\sim} N(0,1) \\ T_1 \overset{\Delta=\Delta_A}{\sim} N\left(\dfrac{\Delta_A}{\left\{\bar{\pi}(1-\bar{\pi})(\frac{1}{n_1}+\frac{1}{n_2})\right\}^{1/2}}, \dfrac{\pi_1(1-\pi_1)+\pi_2(1-\pi_2)}{2\bar{\pi}(1-\bar{\pi})} \right) \bar{\pi} = \frac{\pi_1+\pi_2}{2} \end{cases}$
- $T_2 = \dfrac{p_1 - p_2}{\sqrt{\frac{p_1(1-p_1)}{n_1} + \frac{p_2(1-p_2)}{n_2}}}$

- $$\begin{cases} T_2 \overset{\Delta=0}{\sim} N(0,1) \\ T_2 \overset{\Delta=\Delta_A}{\sim} N\left(\frac{\Delta_A}{\left\{\frac{\pi_1(1-\pi_1)}{n_1}+\frac{\pi_2(1-\pi_2)}{n_2}\right\}^{1/2}}, 1\right) \end{cases}$$

6.3 Arcsin square root transformation for proportions

- $X \sim b(n,\pi), p = \frac{X}{n} \implies \sin^{-1}(p^{1/2}) \sim N\left(\sin^{-1}(\pi^{1/2}), \frac{1}{4n}\right)$
- $T_3 = \frac{\sin^{-1}(p_1^{1/2})-\sin^{-1}(p_2^{1/2})}{\left(\frac{1}{4n_1}+\frac{1}{4n_2}\right)^{1/2}}$
- $$\begin{cases} T_3 \overset{\Delta=0}{\sim} N(0,1) \\ T_3 \overset{\Delta=\Delta_A}{\sim} N\left(\frac{\sin^{-1}(\pi_1^{1/2})-\sin^{-1}(\pi_2^{1/2})}{\left(\frac{1}{4n_1}+\frac{1}{4n_2}\right)^{1/2}}, 1\right) \end{cases}$$