Bayesian design and analysis for clinical trials
– a case study and a learner's perspective

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Overview

1. A case study

2. Learner's perspective

- Treatment B : 희귀병을 치료하기 위한 효소 대체제

- Treatment A : 같은 희귀병을 치료하기 위해 나온 새로운 경구투약이며, 어른 실험자들을 대상으로 아래와 같은 두가지 trial이 이루어졌으며 모두 긍정적인 결과가 나왔음.
  - Trial 1 : treatment A의 위약에 대한 superiority trial
  - Trial 2 : treatment A의 treatment B에 대한 non-inferiority trial

- 하지만 소아들에 대해서는 어른들의 결과를 확장하기에는 무리가 있음.

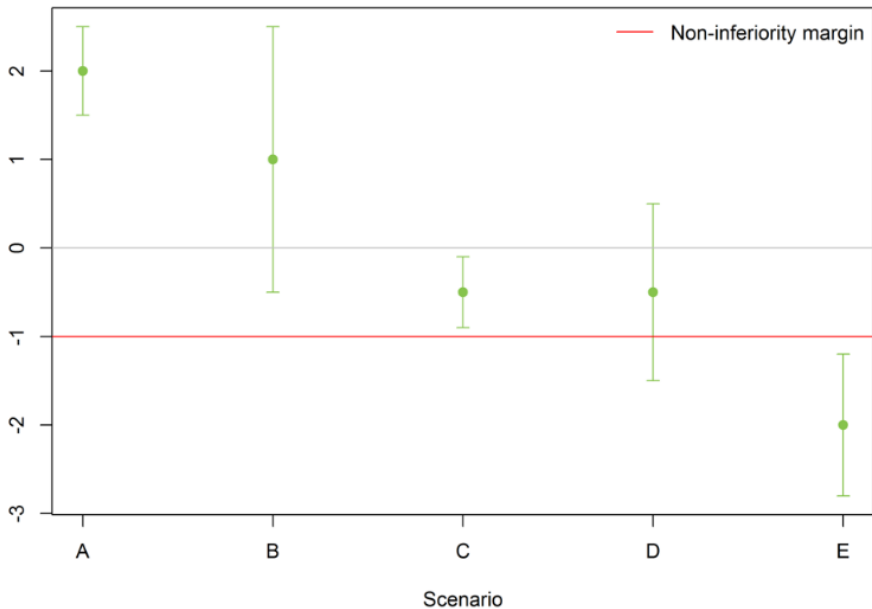- 이 희귀병은 소아들에게 있어서는 더 희귀함 - 피실험자 수에 제한이 있음.

Superiority trial

- $H_0 : \mu_1 \leq \mu_2$ vs $H_1 : \mu_1 > \mu_2$
- 효과의 차이가 매우 작을 경우, superiority를 보이기 위한 n이 매우 커야함
- 효과가 거의 같거나 살짝 부족할 경우, n이 아무리 커도 superiority을 보일 수 없음

Non-inferiority trial

- $H_0 : \mu_1 < \mu_2$ vs $H_1 : \mu_1 \geq \mu_2$
- 새로운 treatment가 기존의 것보다 열등하지 않음을 테스트함
- 새로운 treatment가 다른 장점이 있을경우 유용함(e.g. cost, safety)

Possible outcomes of an non-inferiority trial

소아(Pediatric) 대상 임상시험 설계

- Non-inferiority design for treatment A vs treatment B

- Treatment A : $2n_p$ patients, $A_1, ..., A_{2n_p}$
- Treatment B : n_p patients, $B_1, ..., B_{n_p}$

- $Y_i = \frac{A_{2i-1} + A_{2i}}{2} - B_i$, i=1,2,...,$n_p$
  - $Y_i \sim N(\mu, \sigma^2)$ 가정
  - let $\mu_p = \frac{1}{n_p} \sum_{i=1}^{n_p} Y_i$

어른(Adult) 대상 과거 임상시험 결과

- Non-inferiority design for treatment A vs treatment B

- Treatment A : 70 patients, mean -6.17, SD 14.1
- Treatment B : 39 patients, mean -3.01, SD 10.5

- $\mu_0 = -2.83, \quad \sigma_0 = \sqrt{1.5} * 15$(conservative SD estimator), $\quad n_A$=35

A case study - statistical models and assumptions

- μ 와 σ^2에 대하여 informative conjugate prior 설정
  - $\mu \sim N(\mu_A, \sigma^2/k_0), \quad \sigma^2 \sim IG(\nu_0, \sigma_0^2)$

- ν_0가 ∞인 경우, $\sigma^2 = \sigma_0^2$이며, $\mu|Y \sim N(\mu_n, \sigma^2/k_0)$이 된다.
  - $\mu_n = \frac{k_0}{k_0+n_p}\mu_A + \frac{n_p}{k_0+n_p}\mu_p$
  - $k_n = k_0 + n_p$

- $\nu_0 < \infty$ 인 경우, $p(\mu|Y) \overset{\mu}{\propto} [1 + \frac{k_n(\mu-\mu_n)^2}{\nu_n\sigma_n^2}]^{-\frac{\nu_n+1}{2}}$ 이 된다.
  - $\mu_n = \frac{k_0}{k_0+n_p}\mu_A + \frac{n_p}{k_0+n_p}\mu_p$
  - $k_n = k_0 + n_p$
  - $\nu_n = \nu_0 + n_p$
  - $\sigma_n^2 = \frac{1}{\nu_n}[\nu_0\sigma_0^2 + \sum_{i=1}^{n_p}(Y_i - \mu_p)^2 + \frac{k_0 n_p}{k_0+n_p}(\mu_p - \mu_A)^2]$

- k_0 : 0(non-informative)와 n_A(full extrapolation) 사이 값이며, 편의상 $\nu_0 = k_0$로 설정

A case study - power calculation

Non-inferiority trial modeling

- Non-inferiority margin M=10
  - Estimated effect size for treatment B ~ 22.5
  - The largest clinically acceptable difference $\sim 50\%$

- $H_0 : \mu \geq M$ vs $H_1 : \mu < M$ (μ : mean difference)

Non-inferiority trial modeling - Frequentist

- 1-sided test with α=0.025
- 85% desired power
- 10% dropout rate
- Common SD : 15

- If true mean difference is -2.83, need 63 subjects
- If true mean difference is 0, need 102 subjects
- 계산 방법
  1. $\bar{X}_A - \bar{X}_B \sim N(\mu, \frac{675}{2n})$
  2. μ의 α=0.025 신뢰구간 = $[(\bar{X}_A - \bar{X}_B) - 1.96\sqrt{\frac{675}{2n}}, \quad (\bar{X}_A - \bar{X}_B) + 1.96\sqrt{\frac{675}{2n}}]$
  3. $P((\bar{X}_A - \bar{X}_B) < 10 - 1.96\sqrt{\frac{675}{2n}}) = 0.85$ 가 되는 n 구하기
  4. n에 10/9 곱하기

Non-inferiority trial modeling
- Non-inferiority margin M=10
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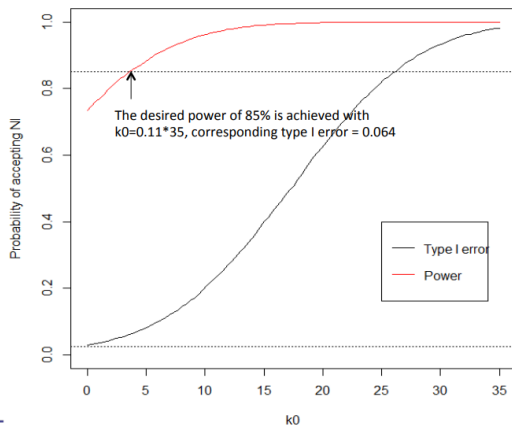- $H_0 : \mu \geq M$ vs $H_1 : \mu < M$ (μ : mean difference)

Non-inferiority trial modeling - Bayesian
- 총 피실험자 50명인 경우를 생각. 즉 n_P=15
- adult trial 결과에서 정보를 많이 가져올수록 Type 1 error rate가 증가한다.
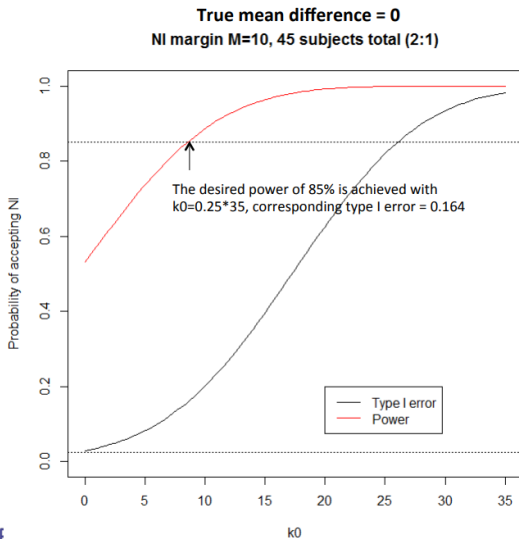- 정보를 얼마나 가져와야 할까? 즉 a=$\frac{k}{n_A}$ ($0 \sim 1$) 을 몇으로 해야 할까?

True mean difference = -2.83

NI Margin M=10,45 subjects, 2:1

The desired power of 85% is achieved with
k0=0.11*35, corresponding type I error = 0.064

Probability of accepting NI

Type I error
Power

k0

True mean difference = 0
NI margin M=10, 45 subjects total (2:1)

Bayesian analyses in US regulatory settings

- CDRH has taken the lead since launching the Bayesian Effort in 1998

- Devices pose unique opportunities for Bayesian design and analyses
  - Typically a lot of prior information available
  - Mechanism of action is physical and local
  - Devices usually evolve in small steps rather than groundbreaking

- Dr. Greg Campbell: CDRH's Bayesian Champion

- Guidance document "Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials" issued in Feb 2010

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Bayesian workshop

- "Can Bayesian Approaches to Studying New Treatments Improve Regulatory Decision-Making?"
  - Held May 20-21, 2004 at NIH

- Jointly sponsored and planned by FDA and Johns Hopkins University

- Presentations by Janet Woodcock, Bob Temple, Steve Goodman, Tom Louis, Don Berry, Greg Campbell, 3 case studies and panel discussions

- August 2005 issue of *Clinical Trials* devoted to this workshop

Janet Woodcock introductory presentation

- First example on the evaluation of antibiotics
  - "Extensive development program wherein they are studied for every indication separately….for all of the classical sites that you can get an infection".

  - "Antibiotic development has really slowed in this country.... concerned about a crisis in availability of new antibiotics with the development of antibiotic resistance that is occurring".

  - "We are starting to evaluate how knowledge about two different things, two types of prior knowledge, could be extrapolated within an antibiotic development program to where you have that needed level of certainty, but not necessarily the traditional number of trials and types of evidence that you had previously. Yet you would be just as comfortable about the effectiveness of this drug".

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Janet Woodcock introductory presentation

- "*In vitro* evidence for antibiotic effectiveness against a certain organism."

- "More importantly, it is possible through medical reasoning to extrapolate results from one trial and one site – take pneumonia – and them as supporting evidence for additional sites, such as sinusistis or infections of other respiratory sites".

- Oncology: extrapolate results for related but different types of cancer?

Janet Woodcock introductory presentation

- Second example on replacement therapies
  - "Replacement therapy is basically putting back something that is missing".

  - "I could not find any examples where the molecule, that replacement molecule, was delivered intact and functional to the site of action in the body where it did not work".

  - "With deficiency states, the challenge is getting a molecule to act at the site where it needs to act, and we have a tremendous body of prior knowledge that tells us if we are able to do that, it is going to work".

- Many rare diseases are such "deficiency diseases".

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My take-home messages

- Bayesian approach potentially very useful
  - Dr. Richard Simon from NCI "Bayesian methods, in my experience, really have a major contribution to make when there is prior information or prior assumptions that need to be incorporated into the analysis. Not some subjective prior of the investigator that nobody really cares about anyway, but priors based on data, or on assumptions shared by most stakeholders."

- FDA (not just CDRH) open minded and willing to be innovative

- Need to be evaluated on a case-by-case basis

- Traditional performance metrics such as Type I error rate and Power shall still be assessed via simulation

Discussion

- Where are we in terms of the use of Bayesian design and analyses for (late-phase) clinical trials?
  - Early-phase (e.g., dosing finding) more established
  - Adaptive Bayesian design gaining popularity
  - Anything else?

- What are the most promising areas that may benefit most from such designs?
  - Use adult trial data to augment pediatric study design and analysis
  - Oncology: extrapolate results for related but different types of cancer?
  - Things with strong prior knowledge of success?

- What can we do to facilitate such use?

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