Optimal Two-Stage Drug Screening Designs Based on Continuous Endpoints

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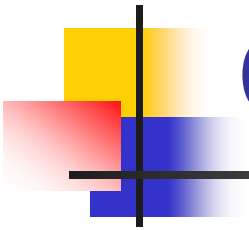


Outlines

- Introduction
- Optimal Drug Screening Designs
  - Optimal Design
  - Minimax Design
- Examples
- Discussion and Summary

Introduction

- Annual spending on biomedical research nearly doubled in the USA between 1994 and 2003, reaching US$94.3 billions
- The number of new drugs making it to the market has declined

Introduction

- Only one out of 10,000 candidates screened in labs will survive to the market launch despite of a better understanding of disease etiology and advance in medical technology
- Success rate of phase III trials has fallen by 30%
- 60 % of drugs in clinical development falter

Introduction

- Cancer clinical trials based on anti-tumor activity
  - Simon two-stage design (1989)
  - Multi-stage design
    - Ensign, et al (1994)
    - Chen (1997)
    - Chen and Ng (1998)
    - Sargent and Goldberg (2001)

Introduction

- Other therapeutic areas
  - Antihypertensive agents (Sitting DBP)
  - Antidepressant agents (HAM-D)
  - Anti-diabetic agents (HbA1c)
  - Anti-asthma agents (FEV1, PEFR)
  - NSAIDs (visual analog in pain score)
  - …
  - Continuous endpoints

Introduction

- Objectives of standard phase II program
  - Proof of concept of efficacy
  - Determination of dose range
    - Minimal effective dose
    - Maximal effective
  - Identification of dose response

Introduction

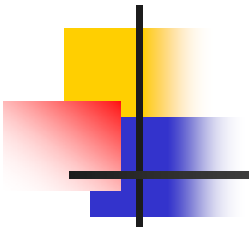
- Standard phase II program
  - Titration studies with or without a concurrent placebo group
  - Randomized parallel-group design
    - Several doses of investigational drugs
    - A concurrent placebo group, may be with a active control for assay sensitivity
    - Comparisons with placebo group with adjustment of p-value

Introduction

- Standard phase II program
  - Several hundred to thousand patients
  - 1-3 years to complete
  - Fail to
    - Show the efficacy
    - Dose response relationship

Introduction

- Reasons
  - Not gone through clinical pilot screening for proof of the concept of efficacy
- For conventional primary endpoints such as DBP, HbA1c, HAM-D, the target for efficacy has been established in these therapeutic areas



Introduction

- Two-stage drug screening designs based on continuous endpoints
  - An efficient and effective means for proof of concept of efficacy during early clinical development
  - Minimize expected sample size subject to constraints upon
    - Type I error rate
    - Type II error rate

Optimal Drug Screening Designs

$X_i \sim N(\mu, \sigma^2)$, i=1,...,n

Hypothesis of interest

$H_0 : \mu \le \mu_0$ vs. $H_a : \mu > \mu_1$,

where μ_0: pre-specified mean level of no efficacy

and μ_a: pre-specified mean level of efficacy

Denote α and β as overall type I and type II error rate

Optimal Drug Screening Designs

- Two-stage optimal drug screening designs
  - Multi-center trials
  - After n_1 patients are enrolled at the 1st stage, eliminate the drug for further consideration if the sample mean of the 1st stage is less than some critical value C_1
  - Otherwise, proceed to 2nd stage
  - If the overall sample mean based on n_1+n_2 patients $< C_2$, reject the drug, otherwise, the concept of efficacy for the drug is proved for further investigation

X_1

Optimal Drug Screening Designs

- Denote X_1, X_2, and Y the sample means of the first stage based on n_1 patients, the overall sample mean based on n_1+n_2 patients, and the sample mean of the second stage based on n_2 patients respectively, where

$$X_1 = \frac{\sum_{i=1}^{n_1} X_i}{n_1}, \quad X_2 = \frac{\sum_{i=1}^{n_1+n_2} X_i}{n_1+n_2}, \text{ and } \quad Y = \frac{\sum_{i=n_1+1}^{n_1+n_2} X_i}{n_2}$$

Optimal Drug Screening Designs

The probability of failure to reject H_0 with true mean level μ is given as

$$\varphi(\mu,\sigma,n_1,n_2,C_1,C_2)$$

$$=P_\mu(\bar{X}_1<C_1)+\int_{C_1}^{\infty} f_\mu(x)P_\mu(\bar{X}_2<C_2)dx$$

$$=P_\mu(\bar{X}_1<C_1)+\int_{C_1}^{\infty} f_\mu(x)P_\mu\{\bar{Y}<C_2(n_1+n_2)/n_2-x(n_1/n_2)\}dx,$$

$$=\Phi\left(\frac{C_1-\mu}{\sigma/\sqrt{n_1}}\right)+\int_{C_1}^{\infty}\frac{1}{\sqrt{2\pi\sigma^2/n_1}}\exp\left(-\frac{(x-\mu)^2}{2\sigma^2/n_1}\right)\Phi\left(\frac{C_2(n_1+n_2)/n_2-xn_1/n_2-\mu}{\sigma/\sqrt{n_2}}\right)dx$$

Optimal Drug Screening Designs

- The overall type I error rate
  - $\alpha = 1 - \varphi(\mu_0, \sigma, n_1, n_2, C_1, C_2)$
- The overall type II error rate
  - $\beta = \varphi(\mu_1, \sigma, n_1, n_2, C_1, C_2)$
- The expected sample size
  - $EN(\mu_0) = n_1 + PET$

$$= n_1 + \{1 - P_{\mu_0}(\bar{X}_1 < C_1)\} n_2.$$

Optimal Drug Screening Designs

Theorem

Given μ_0, μ_1 σ, α, and β and if n^*_1, n^*_2, C^*_1, C^*_2 is a solution of the constraints

$\alpha=\varphi(\mu_0,\sigma,n_1,n_2,C_1,C_2)$, $\beta=\varphi(\mu_1,\sigma,n_1,n_2,C_1,C_2)$, and minimizes the expected sample size, then

$(n^*_1, n^*_2, C^*_1+c, C^*_2+c)$ is also a solution of

$\alpha = 1 - \varphi(\mu_0+c, \sigma, n_1, n_2, C_1, C_2)$,

$\beta = \varphi(\mu_1+c, \sigma, n_1, n_2, C_1, C_2)$, and minimizes the expected sample size $n_1+\{1-P_{\mu_0+c}(\bar{X}_1<C_1)\}n_2$.

for any c

Optimal Drug Screening Designs

- For each value of total sample size n and each value of n_1 in the range of (1, n-1), the critical values C_1 and C_2 are determined to satisfy the two constraints of type I and II error rates and to minimize the expected total sample size when $\mu = \mu_0$.

Optimal Drug Screening Designs

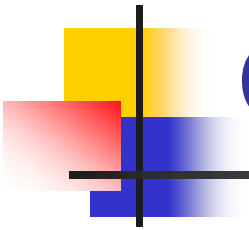
- For each value of n and each value of n_1 in the range of (1, n-1), we use the *Splus* function "NLMIN" which finds a local minimum of a nonlinear function using a general quasi-Newton optimizer (Dennis and Mei, 1979; Dennis, Gay, and Welsch, 1981) to find all values of C_1 and C_2, which satisfied the two constraints α and β.

Optimal Drug Screening Designs

The expected total sample size when $\mu = \mu_0$ is calculated with respect to each (n_1, n_2, C_1, C_2).

We then choose the values of (n_1, n_2, C_1, C_2), which minimizes the expected sample sizes over n.

The search over n ranges from a lower value of about $n = [\sigma/(\mu_1 - \mu_0)]^2 \times [z_\alpha + z_\beta]^2$, which is the sample size calculated by the traditional method for the one-sample problem



Optimal Drug Screening Designs

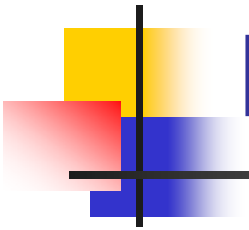
- Two-stage minimax drug screening designs
  - The optimal two-stage drug screening designs does not necessarily minimize the maximum sample size subject to the error probability constraints
  - Minimize the maximum sample size

Examples

- Two-stage drug screening design for $\mu_0=4$, $\mu_1=10$, $\sigma=13$

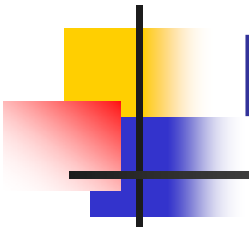
Optimal design

α	β	n_1	n_2	C_1	C_2	$EN(\mu_0)$	$PET(\mu_0)$	n'	n''
.10	.10	15	20	4.8	6.6	23.1	0.60	32	132
.05	.20	12	23	5.9	7.3	19.0	0.70	31	118
.05	.10	18	29	5.4	6.9	27.3	0.68	42	164
Minimax									
.10	.10	17	15	4.4	6.9	23.8	0.54		
.05	.20	14	16	4.8	7.8	20.6	0.59		
.05	.10	19	24	5.0	7.2	27.9	0.63		



Examples

- $\mu_0=4$, $\mu_1=10$, $\sigma=13$, $\alpha=0.05$, $\beta=0.20$
- The first stage needs to recruit $n_1=12$ patients
- If the sample mean of the first stage is less than $C_1=5.9$, eliminate the drug for further consideration
- Otherwise, continue to recruit additional 23 patients for the second stage



Examples

- If the overall sample mean based on 35 patients (12+23) is less than 7.3, then eliminate the drug for further consideration
- Otherwise, claim that the concept of efficacy for the drug is proved and it will move to the late phase II/III stage of clinical development

Examples

- If $\mu_0=14$, $\mu_1=20$, $\sigma=13$, $\alpha=0.05$, $\beta=0.20$
  - By Theorem, the proposed two-stage design is location invariant such that the sample size depends only upon the difference of μ_0 and μ_1, and NOT on the absolute values of μ_0 and μ_1
  - n_1 and n_2 will be the same as for the case of $\mu_0=4$, $\mu_1=10$, $\sigma=13$, $\alpha=0.05$, $\beta=0.20$
  - $C_1= 15.9$ and $C_2=17.3$

Discussion and Summary

- An optimal two-stage design is proposed for drug screening based on
  - proof of the concept of efficacy
  - continuous endpoints
- Minimize the expected sample size
- Shorten the trial duration
- Efficient and cost-effective design to eliminate the candidates without efficacious potential

Discussion and Summary

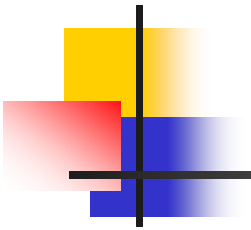
- The proposed optimal two-stage drug screening design can be used after the initial safety assessment of the drug in health subjects is completed
- The required sample sizes are very close to the usual sample sizes for the late phase I safety trials in the targeted patient population
- It can be employed in conjunction with the late phase I trials

Discussion and Summary

- The endpoints for the proposed optimal two-stage drug screening designs should be the same as those for phase III trials
- To minimize the bias, a placebo run-in period should be employed to estimate the placebo effect and served as the internal control
- The change (percent) from baseline should be used as the primary efficacy endpoint

Discussion and Summary

- The proposed ACCESS Act
  - Tier 1 approval of an investigator drug, device, or biological product after it has completed phase 1 safety testing
- Our proposed optimal two-stage drug screening designs provides an efficient and effective means for initial assessment of efficacy during phase I stage



Thank You