National Translational Medicine and
Clinical Trial Resource Center
國家轉譯醫學與臨床試驗資源中心

OPTIMAL TWO-STAGE DESIGNS FOR PHASE II CLINICAL TRIALS

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CONTROLLED CLINICAL TRIALS 1989; 10:1-10

SUMMARY

- **研究目的**

  考慮到研究成本以及風險，本研究希望能將

  Phase I、 Phase II的臨床試驗人數降到最低。

- **方法**

  主要利用Type I、 Type II error來控制樣本數。

- **結論**

  該方法的使用確實有達到降低成本及風險的目的，

  但也有其他方法可以達到相似的效果。

OUTLINE

1. **Introduction**
   - ✓Phase I Clinical Trials
   - ✓Phase II Clinical Trial
   - ✓Two-stage Design
2. **Optimal Two-Stage Designs**
3. **Discussion**

PHASE I CLINICAL TRIALS

Primary Objective

- ✓提供治療的最大耐受劑量
  - 大多數的癌症治療方法必須藉由給予最大劑量來發揮最大治療功效
- ✓很少提供的抗腫瘤活性(antitumor activity)的訊息

PHASE II CLINICAL TRIAL

Primary Objective

- ✓藉由了解一個 new anticancer drug 是否具有足夠的活性去對抗特定型態的腫瘤，來評斷該 drug 是否有未來的發展性(是否需要進行後續的研究)。

- ✓後續研究:
  - Combining the drug with other drugs
  - Evaluation in patients with less advanced disease
  - Initiation of phase III studies in which survival results are compared to those for a standard treatment.

PHASE II CLINICAL TRIAL

Primary Endpoint

- ✓受試病患中，腫瘤至少縮小50%的機率

  (Proportion of patients whose tumors shrink by at least 50%)

- ✓有時反應的耐久性也是研究的重點之一

- ✓沒有針對 drug 的有效性(effectiveness)、

  或在治療該疾病中扮演什麼樣的角色做評論。

WHY NEED MULTI-STAGE DESIGN ?

現實考量

- ✓研究是否繼續，必須經過評估
  - ✓評估病人對藥物的反應
  - ✓評估病人自身的條件是否還適合繼續留在研究
- ✓評估病人對藥物的反應，可能需要數週或數月的觀察
- ✓許多案例 (病人以及醫生) 對終止研究是無法接受的

因此，考慮到成本 (COST)、以及受試者以及研究者的感受，即使越多的 stages 對研究的效率越好，但 two-stage designs 是大家最能接受的選擇。

OPTIMAL TWO-STAGE DESIGNS

True response probability of drug, p

First stage ($\mathrm{H}_0 : p \leq p_0$ **)**

P_0 : uninteresting level

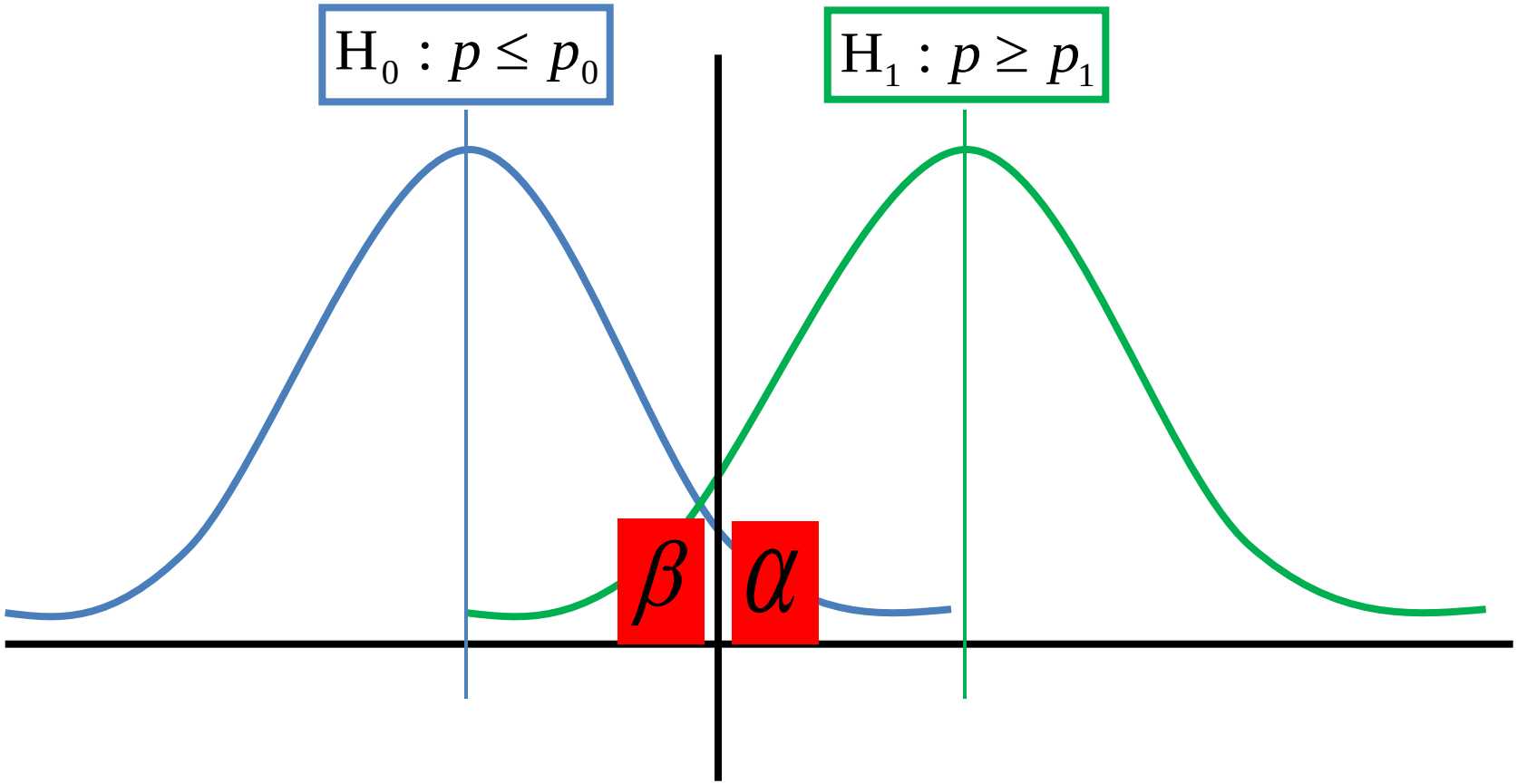
✓如果 H_0是真的，那麼我們要求 p-value $< \alpha$ ，來證明該藥物的有足夠的保證，應該被接受進入下一階段進行其他的臨床試驗

Second stage ($\mathrm{H}_1 : p \geq p_1$ **)**

P_1 : target level

✓如果H_1 是真的，那麼拒絕該藥物進入下一階段進行其他臨床試驗的p-value $< \beta$

p : true response probability of drug



除了以上2個限制，研究者也希望盡量減少以低活性(low activity)藥物治療的患者人數

OPTIMAL TWO-STAGE DESIGNS

Richard Simon 提出的 optimal two-stage designs，就是在控制 type 1 以及 type 2 errors (α, β) 的前提下，以最小的預期樣本數進行研究，其中，參與 first stage 的受試者人數越少越好(first stage 的風險最高)。

- 設定 p_0, p_1, α, β 之後，我們可以得到:

	First stage	Second stage
受試者人數	n_1	n_2
Stage 結束時 應觀察到有反應的 標準受試者人數	r_1 If response $< r_1$ 實驗會被終止	r If response $\leq r$ 藥物會被拒絕

PET

✓研究在 first stage 結束後終止的機率

EN

✓Expected Sample Size $\quad \mathrm{EN} = n_1 + (1 - \mathrm{PET})n_2$

OPTIMAL TWO-STAGE DESIGNS

該藥物被拒絕的機率:

$$B(r_1;p,n_1) + \sum_{x=r_1+1}^{\min[n_1,r]} b(x;p,n_1)\, B(r - x;p,n_2)$$

OPTIMAL TWO-STAGE DESIGNS

- Step 1: 設定 p_0, p_1, α, β
- Step 2: 設定 n，尋找最適當的 n_1
  - ✓ 利用公式 $\bar{p}(1-\bar{p})\left[\frac{z_{1-\alpha}+z_{1-\beta}}{p_1-p_0}\right]^2$ 出最大的 n，再往下修
- Step 3: 利用 p_0, α, β, n_1 求出 r_1
- Step 4: 利用 $p_1, \alpha, \beta, n, n_1, r_1$ 求出 r
- Step 5: test n, n_1, r_1, r 是否符合 設定的 type 1 以及 type 2 errors

All calculations are based on exact binomial probabilities

OPTIMAL TWO-STAGE DESIGNS

- Optimal designs achieve reductions in EN by having smaller first stages than the minimax designs

  (Exposes few patients to an inactive treatment at first stage)

- Minimax design is more attractive than optimal design (with the minimum expected sample size) when the difference in expected sample sizes is small, the patient accrual rate is low (PET is high) and patient population is very heterogeneous

two-stage design

Table 1 Designs for $p_1 - p_0 = 0.20$[a]

		Optimal Design				Minimax Design			
		Reject Drug if Response Rate				Reject Drug if Response Rate			
p_0	p_1	$\leq r_1/n_1$	$\leq r/n$	EN(p_0)	PET(p_0)	$\leq r_1/n_1$	$\leq r/n$	EN(p_0)	PET(p_0)
0.05	0.25	0/9	2/24	14.5	0.63	0/13	2/20	16.4	0.51
		0/9	2/17	12.0	0.63	0/12	2/16	13.8	0.54
		0/9	3/30	16.8	0.63	0/15	3/25	20.4	0.46
0.10	0.30	1/12	5/35	19.8	0.65	1/16	4/25	20.4	0.51
		1/10	5/29	15.0	0.74	1/15	5/25	19.5	0.55
		2/18	6/35	22.5	0.71	2/22	6/33	26.2	0.62
0.20	0.40	3/17	10/37	26.0	0.55	3/19	10/36	28.3	0.46
		3/13	12/43	20.6	0.75	4/18	10/33	22.3	0.50
		4/19	15/54	30.4	0.67	5/24	13/45	31.2	0.66
0.30	0.50	7/22	17/46	29.9	0.67	7/28	15/39	35.0	0.36
		5/15	18/46	23.6	0.72	6/19	16/39	25.7	0.48
		8/24	24/63	34.7	0.73	7/24	21/53	36.6	0.56
0.40	0.60	7/18	22/46	30.2	0.56	11/28	20/41	33.8	0.55
		7/16	23/46	24.5	0.72	17/34	20/39	34.4	0.91
		11/25	32/66	36.0	0.73	12/29	27/54	38.1	0.64
0.50	0.70	11/21	26/45	29.0	0.67	11/23	23/39	31.0	0.50
		8/15	26/43	23.5	0.70	12/23	23/37	27.7	0.66
		13/24	36/61	34.0	0.73	14/27	32/53	36.1	0.65
0.60	0.80	6/11	26/38	25.4	0.47	18/27	24/35	28.5	0.82
		7/11	30/43	20.5	0.70	8/13	25/35	20.8	0.65
		12/19	37/53	29.5	0.69	15/26	32/45	35.9	0.48
0.70	0.90	6/9	22/28	17.8	0.54	11/16	20/25	20.1	0.55
		4/6	22/27	14.8	0.58	19/23	21/26	23.2	0.95
		11/15	29/36	21.2	0.70	13/18	26/32	22.7	0.67

(α, β): (0.10, 0.10)
(0.05, 0.20)
(0.05, 0.10)

two-stage design

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(0.05, 0.20)
(0.05, 0.10)

DISCUSSION

Gehan EA

- ✓most commonly used design
- ✓First stage of 14 patients
- ✓If no responses are observed in the first stage, then the trial is terminated
  - ✓Second stage of 11 patients

Gehan EA. J Chron Dis 13:346-353, 1961

Schultz JR et al Formula

- ✓Formula for calculating the operating characteristics of general k-stage designs with the possibility of acceptance and rejection at each stage

Schultz JR et al. Biometrics 29:293-300, 1973

Fleming

- ✓Early rejection of a hypothesis occurs only when interim results are quite extreme

Fleming TR et al. Biometrics 35:549-555, 1979

Chang et al

- ✓Early acceptance of the drug is permitted and the expected sample size, averaged over the null and alternative hypotheses, is minimized.

Chang MN et al. Biometrics 43:865-874, 1987

DISCUSSION

- For phase II trials of new drugs against solid tumors, designs with (p_o,p_l) equal to (0.05,0.20), (0.05,0.25), or (0.10,0.25) will often be appropriate.

- In phase II trials, type 1 and type 2 errors are both important. (Cost)

✓ β represents the probability of rejecting a treatment with response rate $\geq p_1$

✓ α represents the probability of failing to reject a treatment with response probability $\leq p_0$

DISCUSSION

- New drugs that provide relatively modest (20%-25%) response rates against these refractory diseases are of interest for further development.

- For pilot studies of combinations, the level $p_I - p_0 = 0.20$ is commonly the degree of difference targeted.

- $p_I - p_0 = 0.15$ is probably the smallest difference that one would consider for a phase II study.

THANK YOU FOR YOUR ATTENTION !!