CT 41: 第二期臨床試驗
Phase II Design

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Phase II (SE, SA)

- Safety and Efficacy Studies (SE)
- Safety-Activity (SA)
- Larger Size (20∼100)
- Carry forward recommended dose from phase I
- Seeking to establish evidence of activity
- Not comparative (II, IIa) vs. comparative (IIb)
- Sometimes controlled
- Several months to 2 years
- Practice for phase 3

目錄

Phase II Design: Introduction

- Looking for evidence of activity,
  with respect to what is already available to subjects.
- “Phase II” is convenient word but loosely defined.
- Piantadosi uses term middle development.

Phase II Design Overview

- feasibility of treatment
- side effects and toxicity
- logistics of administration and cost
- dose finding (lowest dose level with good efficacy)
- Major issue: Is there enough evidence
  of efficacy of the new drug to move to phase III?
- Surrogate markers are often used.
- Usually, one-arm (no comparison)

表 1: When is phase 2 step most critical?

Factors in favor of Phase 2	Factors in favor of skipping Phase 2
Many competing experimental therapies in pipeline	Lack of available therapies for disease (either experimental or approved)
Pessimistic about likelihood of success	Optimistic about likelihood of success
Availability of short-term, easily measured surrogate efficacy outcomes	Efficacy usefully measured by hard clinical outcomes
Highly prevalent disease	Rare disease
Opportunity cost for failed phase 3 trial would be high	Opportunity cost for time required to do phase 2 is high

測驗 1

A disease has a population prevalence of 2%. You have a diagnostic test for the disease that has sensitivity and specificity equal to 0.9. What is the post-test probability that an individual who tests positive has the disease?

1. 0.155
2. 0.431
3. 0.783
4. 0.900

測驗 2

Repeat the previous question with a true disease prevalence of 20%.

1. 0.420
2. 0.531
3. 0.692
4. 0.990

Drug Development Pipeline I

- Let W denote drugs that are worthwhile
- Let W^C denote drugs that are not worthwhile
- Illustration of phase 2 goal:

Drug Development Pipeline II

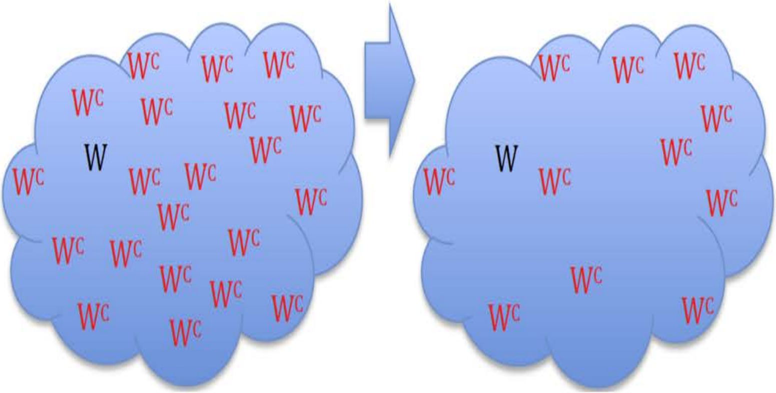

圖 1: 第二期臨床試驗目標

Drug Development Pipeline III

- $P_{\text{ph2}}(W)$: % of truly "worthwhile" drug entering phase 2 stage
- α, β: type I and type II error rates in phase 2
- S_2 indicate that a drug is selected in phase 2 pipeline
- From Bayes Rule, true positive finding from phase 2 is:

$$P(W \mid S_2) = \frac{P(S_2 \mid W)P_{\text{ph2}}(W)}{P(S_2 \mid W)P_{\text{ph2}} + P(S_2 \mid W^c)P_{\text{ph2}}(W^c)} \tag{1.1}$$

$$= \frac{(1-\beta)P_{\text{ph2}}(W)}{(1-\beta)P_{\text{ph2}}(W) + \alpha(1-P_{\text{ph2}}(W))}. \tag{1.2}$$

Drug Development Pipeline IV

- If 2% of drugs entering phase 2 study are truly worthwhile.
- $\alpha = 0.05$, and $\beta = 0.20$, then

$$\frac{(0.80 \times 0.02)}{(0.80 \times 0.02 + 0.05 \times 0.95)} \approx 25\%. \tag{1.3}$$

- Approximate 25%of drugs leaving phase 2 study and entering phase 3 study, are truly worthwhile.

Drug Development Pipeline V

- Phase 2 goal is to enrich phase 3 population with worthwhile drugs
  so that positive findings in phase 3 are highly likely to be true positives:
- If 25% of drugs entering phase 3 study are truly worthwhile.
- $\alpha = 0.05$, and $\beta = 0.20$, then

$$\frac{(0.80 \times 0.25)}{(0.80 \times 0.25 + 0.05 \times 0.75)} \approx 84\%. \tag{1.4}$$

- 84% of drugs leaving phase 3 study,
  i.e. submitted for regulatory approval, are truly worthwhile.

General Dichotomy of Phase II Designs

- Phase II or Phase IIA: any evidence of activity?
  Lower threshold, single arm, fewer subjects
- Phase IIB: evidence of greater efficacy?
  Higher threshold, randomized (multiple arms), more subjects.
- In reality, blurry distinction between these two.

Statistical Setup for Single Arm Phase II I

- All subjects enrolled to new therapy.
- Followed for outcome ("response")
- Response often (forced to be) binary, $Y \in \{0, 1\}$.
- May take time to occur, e.g.
  - tumor shrinkage of X% by 3 months.
  - clinical improvement of symptoms by 6 months.
- Should not take too long.

Statistical Setup for Single Arm Phase II II

- Two motivating questions:
  - What is current response rate to best available therapy? (π_0; historical)
  - What response rate would suggest activity? (π_1)

Phase II with Single Arm: Hypothesis Testing I

- $\pi = P(Y = 1) = P(\text{response})$

$$H_0 : \pi = \pi_0 \quad \text{versus} \quad H_1 : \pi = \pi_1. \tag{1.5}$$

- Reject H_0 = conclude further study warranted
- Do not reject H_0 = conclude no further study warranted

Phase II with Single Arm: Hypothesis Testing II

表2: 假設檢定: 型一誤差與型二誤差

真實的狀況	可能的決策	
	接受 H_0	拒絕 H_0
H_0 為真	(4) 正確決策 特異性 (Specificity)	(1) 型一錯誤 (FP) α 誤差
H_A 為真	(2) 型二錯誤 (FN) β 誤差	(3) 正確決策 敏感度 (Sensitivity)

Phase II with Single Arm: Hypothesis Testing III

- One-sided hypothesis test.
- R: total # of responses
- Estimate π with $\widehat{\pi} = R/n$.
- Reject H_0 if $R/n > r/n$ for some constant r
- What sample size n is required?

Phase II with Single Arm: Normal-based Sample Size

- $H_0 : \pi = \pi_0$ versus $H_A : \pi = \pi_1$.
- Effect size: $\delta = \pi_1 - \pi_0$.
- n: sample size.

$$n = \frac{\left(Z_{1-\alpha} \sqrt{\pi_0 (1 - \pi_0)} + Z_{1-\beta} \sqrt{\pi_A (1 - \pi_1)} \right)^2}{(\pi_1 - \pi_0)^2}. \tag{1.6}$$

Comments on Formula

- Large-sample approximation based on normality assumption.
- Actually easy to calculate “exact” sample size directly using binomial distribution (hopefully get similar results).
- Phase II trials have limited budgets–negotiations are inevitable.
- One of your jobs is to communicate ramifications of different choices.
- Various formulas exist in softwares.

Determining r I

- Reject H_0 if $R/n > r/n$ at the end.
- If sufficiently many subjects respond.
- $\pi_0 = 0.20$ and $\pi_1 = 0.35$
- $\alpha = 0.05$ and $\beta = 0.20$
- one-sided test
- $n = 50$ and $r = 15$ (reject H_0)

$$Pr(R > r \mid \pi = \pi_0 = 0.20) = 0.031 \quad (\text{reject } H_0) \tag{1.7}$$

$$Pr(R > r \mid \pi = \pi_1 = 0.35) = 0.720. \tag{1.8}$$

Determining r II

- So if 15 or more responses (out of $n = 50$), move to phase 3
- Reality check: 95% score-based CI for π is (0.19, 0.44).
- CI lower limit = 0.19 $< \pi_0 = 0.20$
- Evidence not overwhelming.

目錄

Stopping for Futility I

- In one-stage design, all subjects enrolled before decision
- What if no responses after 5, 10, 15 subjects?
- Worthwhile, ethical to continue?
- Motivation for interim futility analyses
- futile = no use in trying
- lack of evidence for activity

Stopping for Futility II

- Simple futility analysis
- First stage:

  assesses likelihood of no responses under H_1.

表3: Stopping for Futility When $R = 0$

subjects enrolled	$P(R = 0 \mid \pi = 0.35)$
1	0.650
2	0.423
3	0.275
4	0.179
5	0.116
6	0.075
7	0.049
8	0.032

Two-stage design (Gehan, 1961)

- Stage One:
  - Enroll initial cohort of n_1 subjects.
  - Stop for futility if no responders
- Stage Two:
  - Otherwise, enroll remaining $n - n_1$ subjects.
  - Conduct standard hypothesis test at end.
- Gehan originally proposed $n_1 = 14$ based upon $H_1 : \pi = 20\%$.
- Circa 1960 (early chemotherapeutic era),

  20% response rate was impressive.
- We can use $n_1 = 7$ based upon larger 35% response rate.

測驗 3

Relative to a one-stage design, adding a futility analysis will generally

1. increase the total type I error rate
2. not change the total type I error rate
3. decrease the total type I error rate

測驗 4

How many unique values of n, i.e. the actual sample size, can a two-stage design actually have, assuming all rules are followed precisely?

1. the actual sample size is pre-specified in advance
2. there are two possible sample size
3. n: enrollment could stop at any point in the trial

Modified Gehan's Designs

- Modified Gehan's Designs
- Continue if $R_1 > 0$ (first stage), $R > r$ (second stage)

$$\text{Type I Error} \tag{2.1}$$

$$= P(R > r, R_1 > 0 \mid \pi = \pi_0) \tag{2.2}$$

$$= \sum_{x=1}^{n_1} P(R > r, R_1 = x \mid \pi = \pi_0) \tag{2.3}$$

$$= \sum_{x=1}^{n_1} P(R - R_1 > r - x, R_1 = x \mid \pi = \pi_0) \tag{2.4}$$

$$= \sum_{x=1}^{n_1} P(R - R_1 > r - x \mid \pi = \pi_0) \times P(R_1 = x \mid \pi = \pi_0). \tag{2.5}$$

表 4: 比較第二期試驗設計: One Stage 與 Modified Gehan

	Type I Error	Power	P (Early Termination)	$\mathcal{E}$(Enrollment)
One Stage	0.061	0.812	0.00	50
Modified Gehan	0.057	0.785	0.21	41

Comments

- Tradeoff: enroll 9 fewer subjects (on average)
  for slight loss of power.
- However, futility analysis is conservative:
  $P(R_1 = 0 \mid \pi = \pi_0) = 0.210$,
  i.e. almost 80% chance of enrolling max possible subjects under H_0
- Possible refinement: new stage 1 stopping rule: $R_1 > r_1$.
  Tune $\{r_1, n_1\}$ to stop when $H_0 : \pi = \pi_0$ appears likely

How to Determine n_1 and n? I

- Determine n_1: denote X = # responses out of n_1 subjects.

$$P(X = 0) = (1 - \pi)^{n_1}. \tag{2.6}$$

- π_0 = minimal efficacy
- If $\pi > \pi_0 \Rightarrow$ investigate the new drug in phase III.
- Control the probability of discarding the new drug early if in fact it is promising.
- n_1 has to satisfy:

$$P(X = 0) = (1 - \pi)^{n_1} \leq \alpha_0, \ \forall \ \pi_{\geq} \pi_0. \tag{2.7}$$

- where α_0 is our tolerance.

How to Determine n_1 and n? II

- $P(X = 0) = (1 - \pi)^{n_1}$ is an deceasing function of π,
- Only need n_1 for

$$(1 - \pi_0)^{n_1} \leq \alpha_0. \tag{2.8}$$

$$\Rightarrow \quad n_1 \log(1 - \pi_0) \leq \log(\alpha_0) \tag{2.9}$$

$$\Rightarrow \quad \text{need} \quad n_1 \geq \frac{\log(\alpha_0)}{\log(1 - \pi_0)} \tag{2.10}$$

- $\pi_0 = 0.20, \alpha_0 = 0.05$

$$n_1 \geq \frac{\log(0.05)}{\log(1 - 0.20)} \approx 14. \quad (\text{round up}) \tag{2.11}$$

How to Determine n_1 and n? III

- Interpretation:
- If see 0/14 responses,

  upper limit of 95% CI on |*pi* is less than 0.2
- 95% sure response rate with new therapy is less than π_0.

How to Determine n_1 and n? IV

- $n_2 = n - n_1$ chosen to give sufficient precision for estimating $|pi$ after all patients observed
- Gehan chooses n_2 after seeing X_1, but most applications fix n_1 and n_2 (or n) in advance.

How to Determine n_1 and n? V

- Gehan determine n: based on precision of 95% CI.
- Want to be 95% sure that the estimate is within $\pm 15\%$ of the minimum $\pi_0 = 0.2$:

$$1.96 \times \left(\frac{0.2 \times 0.8}{2} \right)^{\frac{1}{2}} = 0.15. \tag{2.12}$$

- Solve $n \approx 28$.

How to Determine n_1 and n? VI

- Expected sample size under Gehan design

$$n = \begin{cases} n_1, & \text{with probability } (1-\pi)^{n_1}; \\ n, & \text{with probability } 1-(1-\pi)^{n_1}. \end{cases} \tag{2.13}$$

$$mean(n) = n_1(1-\pi)^{n_1} + (n_1+n_2)\left(1-(1-\pi)^{n_1}\right) \tag{2.14}$$

$$= n_1 + n_2\left(1-(1-\pi)^{n_1}\right). \tag{2.15}$$

目錄

Simon's Two-Stage Design (Simon, 1989)

- Goal: identify design set $\{r_1, n_1, r, n\}$
  that satisfies type I error α and power $1 - \beta$ constraints.
- Lots of such sets exist
- Simon proposed two designs that are best by some definition
  (Simon, Control Clinical Trials, 1989)
- More than 2800 citations currently

Simon's Two-Stage Design: Statistical Considerations I

- Suppose two values $\pi_0 < \pi_1$ are pre-specified
- Divide $\pi \in (0, 1)$ into 3 Regions: Drug is

  ineffective | Indifference region | effective
- If $\pi \leq \pi_0$ then declare

  the drug ineffective with high probability, $1 - \alpha$,

  where α is taken to be small.
- If $\pi \geq \pi_1$, then consider

  the drug for further investigation with high probability, $1 - \beta$,

  where β is taken to be small.
- α and β are generally 0.05 and 0.20.

Simon's Two-Stage Design: Statistical Considerations II

- Find integers n_1, n, r_1, r, with $n_1 < n, r_1 < n_1$, and $r < n$
- Enroll n_1 subjects in the first stage.
  - If r_1 subjects or less respond,
    then declare the treatment a failure and stop.
  - If more than r_1 respond,
    then add $(n - n_1)$ subjects for a total of n subjects.

Simon's Two-Stage Design: Statistical Considerations III

- At the second stage:
  - if the total # that respond among all n subjects is greater than r, then declare the treatment a success.
  - otherwise, declare it a failure.
- stop the trial at stage 1
  - if the # of responses among n_1 is greater than r, then declare the treatment a success.

Simon's Two-Stage Design: Statistical Considerations IV

- X_1 = the # of responses in stage 1 (out of n_1 subjects)
- X_2 = the # of responses in stage 2 (out of $n_2 = n - n_1$ subjects)

$$X_1 \sim Bin(n_1, \pi), X_2 \sim Bin(n_2, \pi) \quad (X_1 \text{ and } X_2 \text{ are ind}). \quad (3.1)$$

Simon's Two-Stage Design: Statistical Considerations V

- Declare the new drug a failure if

$$(X_1 \leq r_1) \text{ OR } \{(X_1 > r1) \text{ AND } (X_1 + X_2 \leq r)\}. \tag{3.2}$$

- The new drug is declared a success if

$$(X_1 > r_1) \text{ AND } (X_1 + X_2 > r). \tag{3.3}$$

Simon's Two-Stage Design: Statistical Considerations VI

- Design constraints

$$P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r)\Big) \leq \alpha, \ \forall \ \pi \leq \pi_0; \quad (3.4)$$

$$P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r)\Big) \geq \beta, \ \forall \ \pi \geq \pi_1. \quad (3.5)$$

Simon's Two-Stage Design: Statistical Considerations VII

- Denote the power function by

$$\Psi(\pi) = P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r) \,\Big|\, \pi\Big). \tag{3.6}$$

- $\Psi(\pi)$ is an increasing function of π for any n_1, r_1, n, r.

Simon's Two-Stage Design: Statistical Considerations VIII

- Therefore, criteria (3.4) and (3.4) are equivalent to

$$P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r) \,\Big|\, \pi = \pi_0\Big) = \alpha, \qquad (3.7)$$

$$P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r) \,\Big|\, \pi = \pi_1\Big) = \beta. \qquad (3.8)$$

Simon's Two-Stage Design: Statistical Considerations IX

- How to calculate $P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r) \Big| \pi \Big)$ for each π?
- By independence of X_1 and X_2:

$$P\Big((X_1 > r_1) \text{ AND } (X_1 + X_2 > r) \Big| \pi \Big) \tag{3.9}$$

$$= \sum_{m_1 > r_1, m_1 + m_2 > r} P(X_1 = m1, X_2 = m2) \tag{3.10}$$

$$= \sum_{m_1 > r_1, m_1 + m_2 > r} P(X_1 = m1)\, P(X_2 = m2). \tag{3.11}$$

Simon's Two-Stage Optimal Design I

- Many combinations of n_1, n, r_1, r satisfy (3.4) and (3.4).
- Optimal Design:

  has smallest expected sample size when $\pi = \pi_0$

  (when the new drug is ineffective)

Simon's Two-Stage Optimal Design II

- The expected sample size when $\pi = \pi_0$

$$\mathcal{E}(n \mid \pi = \pi_0) \tag{3.12}$$

$$= n_1 P(\text{stop at stage 1}) + nP(\text{did not stop at stage 1}) \tag{3.13}$$

$$= n_1 \Big(P(X_1 \leq r_1 \mid \pi = \pi_0) + P(X_1 > r \mid \pi = \pi_0) \Big)$$

$$+ nP(r_1 + 1 \leq X1 < r \mid \pi = \pi_0). \tag{3.14}$$

Simon's Two-Stage Optimal Design III

- Through computer search, the optimal design can be identified.
- Among all sets of n_1, n, r_1, r satisfy (3.4) and (3.4) constraints, identify set that minimizes $\mathcal{E}(n \mid \pi = \pi_0)$
- Minimize number of subjects enrolled when trial should not have been run.
- Simon (1989), Optimal two-stage designs for Phase II clinical trials. Controlled Clinical Trials. 10: 1-10.

Simon's Two-Stage Minimax Design

- Through computer search, the optimal design can be identified.
- Among all sets of n_1, n, r_1, r satisfy (3.4) and (3.4) constraints, identify set that minimizes n.
- Aimed at identifying effective agents using as few patients as possible.

測驗 5

For studying a rare disease in which patient accrual is slow, which of the Simon's design would likely make more sense

1. optimal
2. minimax

Simon's two-Stage Design

- Implemented in `clinfun` package (Seshan, 2015)

目錄

Admissible Two-Stage Designs

- Consider expected cost function for any possible design set satisfying α and β constraints given by

$$C(q, \{r_1, n_1, r, n\}) = qn + (1-q)\mathcal{E}(n \mid \pi = \pi_0) \qquad (4.1)$$

- It is weighted average of maximum sample size and expected sample size under H_0
- Design set n_1, n, r_1, r is called admissible
  if it achieves smallest possible cost
  across all possible design sets for at least one $q \in [0, 1]$.

Simon's Design and Admissible Design

- Simon's optimal design is admissible because it minimizes risk when $q = (?)$
- Simon's minimax design is admissible because it minimizes risk when $q = (?)$
- There are usually other admissible designs that minimize risk for $q \in (0, 1)$.
- Jung et al., 2004

Discussion I

- Phase 2 trials are most often futility trials.
- Goal is to prune inefficacious treatments
- Could trial stop for efficacy at stage 1? Should it?
- Different implications from stopping early because $R_1 \leq r_1$ and failing to reject H_0 because $R \leq r$
- Nothing special about two stages.
- More stages possible.

Discussion II

- Strict sample sizes and adherence to interim analyses may be difficult to adhere to.
- Causes trial conduct to deviate from trial design and potentially invalidates type I error and power properties.
- Inference is conditional on following design as it is laid out

Inference depends on design: Ex 1 I

- Suppose that we conduct minimax design with $\pi_0 = 0.20$, $\pi_1 = 0.35$, $\alpha = 0.05$, and $1 - \beta = 0.80$:
  $\{r_1, n_1, r, n\} = \{6, 31, 15, 53\}$
- We successfully conclude the trial
  with $R = 16 > r = 15$ responders.

Inference depends on design: Ex 1 II

- Could report p-value:

$$
\begin{aligned}
p \quad & P(R > 15, R_1 > 6 \mid \pi = \pi_0) && (4.2)\\
&= \sum_{x=7}^{31} P(R > 15, R_1 = x \mid \pi = \pi_0) && (4.3)\\
&= \sum_{x=7}^{31} P(R - R_1 > 15 - x, R_1 = x \mid \pi = \pi_0) && (4.4)\\
&= \sum_{x=7}^{31} P(R - R_1 > 15 - x \mid \pi = \pi_0) \\
&\qquad \times P(R_1 = x \mid \pi = \pi_0) && (4.5)\\
&= 0.0498. && (4.6)
\end{aligned}
$$

Inference depends on design: Ex 1 III

```
# Inference depends on design: Ex 1
# Design 1
r1 = 6; n1 = 31; R = 15; n = 53;
p0 = 0.20
sum(pbinom(R - ((r1+1):n1), n - n1, p0, lower.tail = F) *
                  dbinom((r1+1):n1, n1, p0));
[1] 0.04979161
```

Inference depends on design: Ex 2 I

- Adapted from (Lindley and Phillips, 1976).
- Two designs for testing $H_0 : \pi = 0.2$.

Inference depends on design: Ex 2 II

- Design 1:
- Enroll $n = 25$ patients.
- R is binomial.
- Observe $R = 8$ responses.
- p-value is

$$P(R \geq 8 \mid \pi = 0.2) = \sum_{x=8}^{25} \binom{25}{8} (0.2)^x (0.8)^{25-x} \tag{4.7}$$

$$= 0.109. \tag{4.8}$$

```
1 # Inference depends on design: Ex 2
2 pbinom(7 , 25, 0.2, lower.tail = F) # 1-binomial CDF
3 [1] 0.1091228
```

Inference depends on design: Ex 2 III

- Design 2:
- Enroll patients until $f = 17$ non-responders.
- R is negative binomial. Observe $R = 8$ responses.
- p-value is (negative-binomial)

$$P(R \geq 8 \mid \pi = 0.2) = \sum_{x=8}^{\infty} \binom{x+16}{x} (0.2)^x (0.8)^{17} \quad (4.9)$$

$$= 0.0892. \quad (4.10)$$

```
1 # Inference depends on design: Ex 2
2 # Design 2
3 pnbinom(7, 17, 1-0.2, lower.tail = F) # 1 - neg-binom CDF
4 [1] 0.08917126
```

Inference depends on design: Ex 2 IV

- Design 1: $p = 0.109$.
- Design 2: $p = 0.089$.
- If $\alpha = 0.10$ were significance threshold, then same data (but different designs) yield different conclusions.

Likelihood Principle

- In both examples,
  likelihood of final data was equal for both designs.
- Frequentist inference based on what could have occurred
  and not just what did occur.
- Violates likelihood principle:
  inference should be based only upon likelihood function
  and not design.

K-Stage Design (Fleming, 1982)

- Gehan design allows for early termination

  only if new therapy seems ineffective
- Fleming (1982, Biometrics)
- K-stage designs allow for early stopping if
  - treatment appears ineffective
  - or treatment appears overwhelmingly effective
- preserve (approximately) size and power of a single stage design

Practical Uses of Fleming's Designs

- Rarely happens that want more than 2 stages
- Rarely terminate phase II trial early
  because treatment is effective.
- Phase III takes time to develop.
- Phase III is not often ready in time to take advantage of early stopping
- Would like more information before starting phase III.

More Phase II Designs

- Bayesian Single Stage Design

  Sylvester, Biometrics, 1988.
- Bayesian Two-Stage Design

  Herson, Biometrics, 1979.
- Bayesian Two-Stage Design

  Simon and Thall, Controlled Clinical Trials, 1989.

  Simon and Thall, Biometrics, 1994.
- Bivariate Designs (Early Stopping for Response and Toxicity)

  Bryant and Day Biometrics, 1995. Conaway and Petroni, Biometrics, 1995.

R Packages: Phase II Design

- `clinfun`
- `ph2simon`
- `ph2mult`
- `DoseFinding`
- `MCPMod`
- `OneArmPhaseTwoStudy`
- `ph2mult`

目錄

Randomized Controlled Phase II Designs

- Two Arms Design and Multiple Arms Design
- Single Stage and Multiple Stages
- Non-adative Design Adaptive Design

Thanks!