
A Comparison of Approaches for Unplanned Sample Size Changes in Phase II Clinical Trials

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Outline

Background and Introduction

Motivation

Deviation from Planned Sample Sizes in Second Stage

Deviation from planned sample sizes in first stage

Phase II Trials

- ▶ Phase I: Evaluate safety and dose
- ▶ Phase II: Evaluate initial effect to determine phase III trial
- ▶ Phase III: Evaluate efficacy
- ▶ Phase II - Two-stage
 - ▶ Mitigate the risk of exposure
 - ▶ Don't want to “waste” resources

Two-stage Phase II Trial

$$H_0 : p \leq p_0, H_1 : p > p_1$$

1. stage 1: n_1 patients are enrolled
 - ▶ $X_1 \sim \text{Binomial}(n_1, p) = \#$ of successes in first stage
2. If number of responses is r_1 or fewer, trial stopped for futility
3. Otherwise, stage 2: n_2 patients are enrolled ($n_t = n_1 + n_2$ total patients now)
 - ▶ $X_2 \sim \text{Binomial}(n_2, p) = \#$ of successes in second stage
 - ▶ $X_t = X_1 + X_2$
4. If number of responses is r_t or fewer, lack of efficacy concluded
5. Otherwise efficacy concluded
 - ▶ $p_0, p_1, n_1, n_t, r_1, r_t, \alpha, \beta$ are design parameters
 - ▶ n_1, n_t, r_1, r_t are chosen so that type I error rate is less than α and the type II error rate is less than β .

Types of Two-Stage Designs

- ▶ Simon introduced Optimal and Minimax criteria for good designs
 - ▶ Optimal minimizes the expected sample size under H_0
 - ▶ Minimax minimizes the maximum sample size
- ▶ Jung *et al.* introduced Admissible designs
 - ▶ Compromise between Optimal and Minimax
 - ▶ Similar maximum sample sizes as Minimax
 - ▶ Similar expected sample size under H_0 as Optimal
- ▶ Suppose $H_0 : p_0 \leq 0.25$, $H_1 : p_1 > 0.4$, $\alpha = 0.05$, $\beta = 0.2$

Design	n_t	n_1	r_1	r_t	EN ₀	PET ₀
Optimal	71	20	5	23	39.5	0.617
Minimax	60	51	16	20	52	0.886
Admissible	63	25	6	21	41.7	0.561

Deviation from the design

- ▶ Attain different enrollment than planned in first and/or second stage
- ▶ Why would we deviate?
 - ▶ Unanticipated recruitment speed
 - ▶ Unanticipated drop out rates
 - ▶ Delay in communication for multi-center trials
 - ▶ Ethical considerations
 - ▶ Shopping for sponsors
- ▶ Nice properties go out the window
- ▶ Currently, common practice is to treat attained sample size as planned
- ▶ Leads to invalid inference
- ▶ Hypothesis testing is not straightforward

Setting the Scene

- ▶ Goal is to make a decision
- ▶ How do we do this if our attained sample size is different than planned?
- ▶ P-value calculations are complicated - we don't consider these solutions
- ▶ Consider prespecified “redesigns” - recalculating critical values
- ▶ Primary focus on deviation in first stage

Deviation from Planned Sample Sizes in Second Stage

- ▶ Over-enrollment in first stage: perform interim analysis on the planned number of first stage, adjust testing procedure for attained second stage
- ▶ Under-enrollment: just wait
- ▶ Literature exists for point estimation, calculation of p-values when stage II differs (Review: Porcher *et al.*)
- ▶ P-values in two-stage trials depend on planned design and attained data, complicated when attained SS differ than planned [Koyama and Chen]

Koyama and Chen

- ▶ Koyama and Chen, StatMed, 2008
- ▶ Notation:
 - ▶ Planned design parameters: $n_1, n_t, n_2 = n_t - n_1, r_t, \alpha, \beta$.
 - ▶ Attained design parameters:
 $n_1, n_t^*, n_2^* = n_t^* - n_1, r_1, r_t^*, \alpha^*, \beta^*$
- ▶ Let first stage remained as planned and change testing procedure in stage II
- ▶ Calculate new critical value, r_t^* , by finding maximum integer s.t.

$$P[X_2^* \geq r_t^* | X_1 = x_1] \leq P[X_2 \geq r_t | X_1 = x_1]$$
$$X_2^* \sim \text{Binomial}(n_2^*, p_0)$$

Koyama and Chen

- ▶ Results in controlled unconditional type I error rate - new CV gives more conservative conditional type I error rate
- ▶ New critical value depends on number of positive responses

Zeng *et al.*

- ▶ Zeng *et al.*, StatMed, 2015
- ▶ Attempts to maximize unconditional power while controlling type I error
- ▶ r_2^* new stage II critical value and $r_t^* \equiv r_2^* + x_1$
- ▶ Second stage CV is integer that maximizes unconditional power while subject to type I error $\leq \alpha$
- ▶ Theoretically possible, computationally difficult. No closed form solution.
- ▶ Propose normal approximation to ease computation of power
- ▶ Math (Lagrange multipliers, derivatives, substitution, searching over λ s)
- ▶ Solve an ugly equation for r_2^*

Zeng *et al.*

$$\begin{aligned} & \left(\frac{1}{p_0(1-p_0)} - \frac{1}{p_1(1-p_1)} \right) r_2^{*2} - \frac{2n_2^*(p_0-p_1)}{(1-p_0)(1-p_1)} r_2^* + \frac{n_2^{*2}(p_0-p_1)}{(1-p_0)(1-p_1)} - 2n_2^* \log \left(\frac{\lambda a(x_1)}{b(x_1)} \right) = 0 \\ a(x_1) &= \binom{n_1}{x_1} p_0^{x_1} (1-p_0)^{n_1-x_1} \\ b(x_1) &= \binom{n_1}{x_1} p_1^{x_1} (1-p_1)^{n_1-x_1} \end{aligned} \tag{1}$$

λ is the Lagrange multiplier.

Deviation from planned sample sizes in first stage

- ▶ SWOG:
 - ▶ $\alpha = 0.05, \beta = 0.1$
 - ▶ Interim: $H_0 : p = p_1, H_1 : p < p_1$, stop if p-value is significant at 0.02-level
 - ▶ Stage II: $H_0 : p = p_0, H_1 : p > p_0$
- ▶ Green and Dahlberg, StatMed, 1992
 - ▶ Use SWOG, but use attained sample size
 - ▶ Test stage II at 0.055 level
- ▶ Unclear how to generalize
- ▶ Arbitrary and lacks theoretical justification [Li *et al.*]

Deviation from planned sample sizes in first stage

- ▶ Chen and Ng, StatMed, 1998
- ▶ Consider range of sample sizes
- ▶ Search these ranges for the Minimax or Optimal design that satisfy error constraints using the average PET and EN
- ▶ Limitation: attained sample sizes may fall outside of ranges
- ▶ Limitation: average probabilities rather than actual for attained SS

Chang *et al.*

- ▶ Chang *et al.* Biometrics & Biostatistics, 2015
- ▶ Recall: $n_1, n_t, r_1, r_t, p_0, p_1, \alpha, \beta$
- ▶ Notation: n_1^{**}, n_2^{**} - attained sample sizes
- ▶ Notation: s_1, s_t - new critical values
- ▶ Choose s_1 by first using β -spending function

$$\beta(m) = \begin{cases} \beta_1 m / n_1 & \text{if } m \leq n_1 \\ \beta_1 + (\beta - \beta_1)(m - n_1) / n_2 & \text{if } m > n_1 \end{cases}$$

- ▶ Integer s.t. type II error probability given s_1, n_1^{**} is closest to $\beta(n_1^{**})$
- ▶ Choose s_t s.t. type I error $\leq \alpha$

└ Deviation from planned sample sizes in first stage

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