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

Molly Olson
molly.a.olson@vanderbilt.edu
Advisor: Tatsuki Koyama

Vanderbilt University
Department of Biostatistics

June 13, 2017

Outline

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: $n_1, n_t, n_2 = n_t - n_1 r_1, r_t, \alpha, \beta$.
  - 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 λs)
- Solve an ugly equation for r_2^*

Zeng *et al.*

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

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 then 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 $\leq \alpha$

Olson and Koyama

- Select s_1 s.t. $\mathrm{PET}_0^{**} \approx \mathrm{PET}_0$
- Conservative
- Could have done $\mathrm{PET}_0^{**} \leq \mathrm{PET}_0$

Background: Likelihood

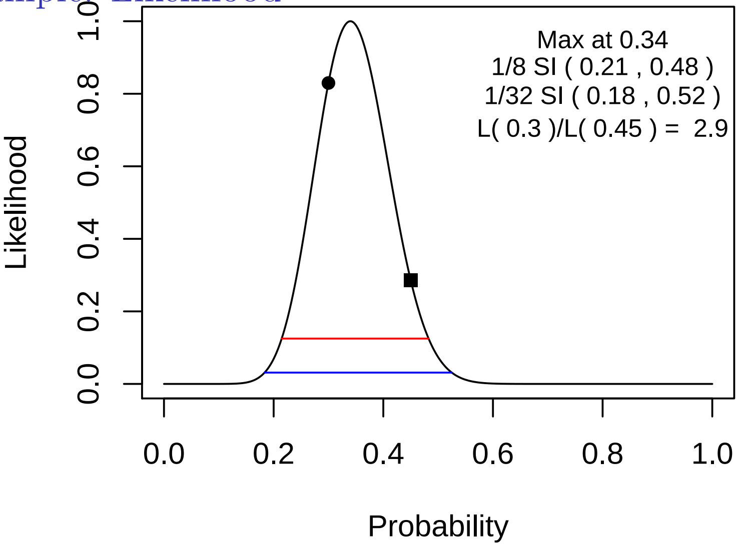
- Law of likelihood: "If $H_1 \Rightarrow P(X = x) = P_1(X)$, $H_2 \Rightarrow P(X = x) = P_2(X)$, then the observation X=x is evidence supporting H_1 over H_2 iff $P_1(X) > P_2(X)$. Likelihood ratio measures strength of evidence.
- Likelihood function:

$$\begin{aligned} \mathrm{L}_n(p) &= P(X|p,n) \\ &= \binom{n}{x} p^x (1-p)^{n-x} \\ &\propto p^x (1-p)^{n-x} \end{aligned} \tag{2}$$

- Likelihood ratio:

$$\mathrm{LR}_n = \frac{\mathrm{L}_n(p_1)}{\mathrm{L}_n(p_2)} \tag{3}$$

Example: Likelihood



Likelihood

- Can calculate probability of observing weak evidence, strong evidence, misleading evidence
- Universal bound of misleading evidence is $\leq 1/k$

Ayers and Blume

- Likelihood two-stage design
- Enroll n_1,
  - $1/k < LR_{n_1}$ ¡ k $\rightarrow$ second stage
  - $LR_{n_1} < 1/k \rightarrow$ stop for futility
  - $LR_{n_1} > k \rightarrow$ stop for efficacy
- Enroll n_2, $LR_{n_t} = LR_{n_1} LR_{n_2}$
  - $1/k < LR_{n_1}$ ¡ k $\rightarrow$ conclude weak
  - $LR_{n_1} < 1/k \rightarrow$ conclude futility
  - $LR_{n_1} > k \rightarrow$ conclude efficacy

Ayers and Blume

- Emulate conventional two-stage designs
- Notation: $k_{a_1}, k_{a_t}, k_{b_1}, k_{b_t}$
- Start with conventional two-stage design, set $k_{b_1}, k_{b_t} = \infty$, redefine k_{a_1}, k_{a_t}

$$
\begin{aligned}
s_1 &= \frac{log(k_{a_1}) - n_1^{**} log\left(\frac{1-p_1}{1-p_0}\right)}{log\left(\frac{p_1(1-p_0)}{p_0(1-p_1)}\right)} \\
s_t &= \frac{log(k_{a_t}) - n_t^{**} log\left(\frac{1-p_1}{1-p_0}\right)}{log\left(\frac{p_1(1-p_0)}{p_0(1-p_1)}\right)}
\end{aligned} \tag{4}
$$

Ayers and Blume

- Can recalculate probability of weak, strong, and misleading evidence, $\mathrm{PET}_0, \mathrm{EN}_0$ under attained
- Minimizes average of error rates
- Type I error rate often below nominal rates

Comparison of methods

- Don't consider added cohorts
- Original total sample size ($n_t^{**} = n_t, n_2^{**} = n_t - n_1^{**}$)
- Original second stage sample size ($n_t^{**} = n_1^{**} + n_2$)

Example

- $n_1 = 17$, $n_t = 41$, $r_1 = 7$, $r_t = 21$, $p_0 \leq 0.4$, and $p_1 \geq 0.6$
- Consider deviations that keep PET at least 50%
- $n_t^{**} = n_t$

Design	s_1	n_1^{**}	PET_0^{**}	EN_0^{**}
Likelihood	6	16	53%	27.8
Chang *et al.*	6	16	53%	27.8
Olson and Koyama	7	16	73%	23.1

Example

Design	s_1	n_1^{**}	PET_0^{**}	EN_0^{**}
Likelihood	10	23	71%	28.2
Chang *et al.*	10	23	71%	28.2
Olson and Koyama	10	23	71%	28.2

Comparison of Methods

- Admissible, Minimax, Optimal
- $\alpha = 0.05, \beta = 0.2$ or $\alpha = 0.1, \beta = 0.1$
- Deviations ± 10
- $n_t^{**} = n_t$ - more realistic

$n_1 = 15, r_1 = 1, n_t = 41, r_t = 7, p_0 = 0.1, p_1 = 0.25$

- s_1 can be different
- Type I error, power, EN_0 similar
- Same design when -6
- Attained << planned, Chang, Likelihood more at risk of low PET

$\mathrm{PET}_0 = 55\%, \mathrm{EN}_0 = 26.7$

Design	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}
Chang *et al.*	13	0	7	0.046	0.830	25%	27.8
OK	13	1	7	0.040	0.771	62%	23.1
Likelihood	13	0	7	0.046	0.830	25%	27.8

$n_1 = 15, r_1 = 1, n_t = 41, r_t = 7, p_0 = 0.1, p_1 = 0.25$

$\mathrm{PET}_0 = 55\%, \mathrm{EN}_0 = 26.7$

Design	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}
Chang *et al.*	23	3	7	0.040	0.785	80%	26.5
OK	23	2	7	0.046	0.827	59%	30.3
Likelihood	23	2	7	0.046	0.827	59%	30.3

Design	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}
Chang *et al.*	5	0	7	0.034	0.671	59%	19.7
OK	5	0	7	0.034	0.671	59%	19.7
Likelihood	5	0	7	0.046	0.827	59%	19.7

$n_1 = 28, r_1 = 15, n_t = 83, r_t = 48, p_0 = 0.50, p_1 = 0.65$

- s_1 inconsistent when under-accrual
- Likelihood can be anticonservative in type I error
- Chang, OK always below nominal type I error
- OK has lower expected sample size

$\text{PET}_0 = 71\%, \text{EN}_0 = 43.7$

Design	n_1^{**}	s_1	s_t	α^{**}	$1 - \beta^{**}$	PET_0^{**}	EN_0^{**}
Chang *et al.*	18	8	7	0.036	0.815	41%	56.5
OK	18	10	7	0.037	0.760	76%	33.6
Likelihood	18	9	7	0.048	0.796	60%	44.5

$n_1 = 22, r_1 = 17, n_t = 39, r_t = 33, p_0 = 0.75, p_1 = 0.90$

- Likelihood type I error and power close to planned design
- Likelihood PET halves when -10
- OK lower than planned error rates when over accrual

$\text{PET}_0 = 68\%, \text{EN}_0 = 27.5$

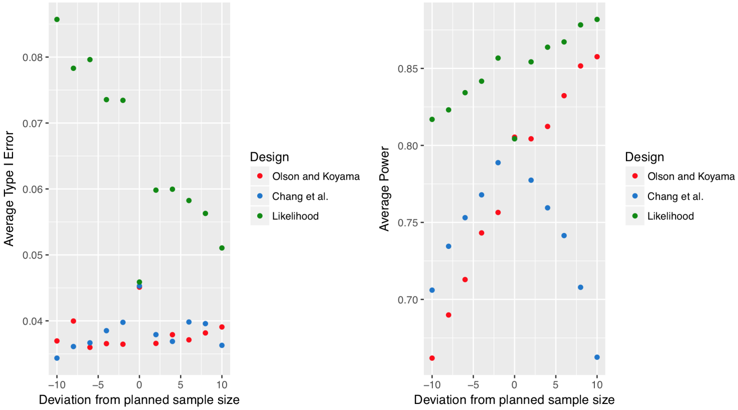
Design	n_1^{**}	s_1	s_t	α^{**}	$1-\beta^{**}$	PET_0^{**}	EN_0^{**}
Chang *et al.*	26	21	33	0.048	0.791	82%	28.4
OK	26	20	34	0.019	0.650	66%	30.4
Likelihood	26	20	33	0.051	0.810	66%	30.4

More Results

- $\alpha = \beta = 0.1$
- Stage I sample size low ($p_0 = 0.05, p_1 = 0.20$)
  - Under-accrual, drop in power and type I error
  - Attained n_1^{**}, $\mathrm{PET}_0^{**} \approx 1$
- Other two cases, similar designs

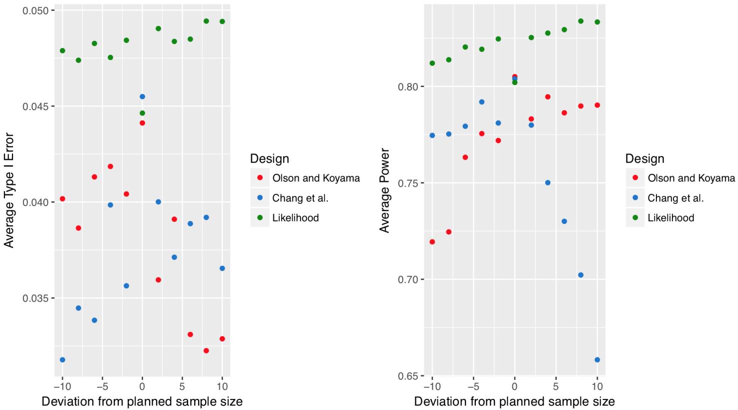
Monte Carlo Simulation

Figure 1: Average error rates of 20 two-stage designs when $n_t^{**} = n_1^{**} + n_2$. Number of simulations = 10,000



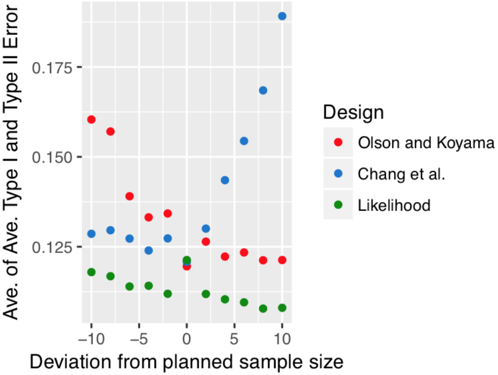
Monte Carlo Simulation

Figure 2: Average error rates of 20 two-stage designs when $n_t^{**} = n_t$. Number of simulations = 10,000



Monte Carlo Simulation

Figure 3: Average of average error rates of 20 two-stage designs when $n_t^{**} = n_t$. Number of simulations = 10,000



Discussion

- Calculation of p-values is hard
- Could calculate ignoring sample path - may have a different decision
- Why can't we just wait for stage I sample size?
- Why do we want to keep the original total sample size the same?
  - Resources
  - Simulation results
  - Can result in a one stage design if don't

Big picture results

- Chang *et al.* and OK differ when extreme deviations
- OK and Likelihood most similar, especially over-accrual
- s_1 usually within a difference of 1

Recommending a design

- Depends on statistical approach
- Do you want to abandon hypothesis testing?
- "Hypothesis testing procedures do not place any interpretation on the numerical value of the LR. The extremeness of an obsevation is measured, not by the magnitude of the LR, but by the probability of observing a likelihood ratio that large or larger. It's the tail area, not the likelihood ratio, that is meaningful quantity in hypothesis testing," Blume, 2002
- If yes, Likelihood design
- If no, OK design

Advantages of Likelihood design

- Recall that we restricted the Likelihood design
- Add cohorts
- Inference is more straightforward
- Generalizable

Concluding Thoughts

- OK design and Likelihood are highly competative when PET above 50%
- One may be more favorable over another depending on hypotheses
- Attained designs able to accomodate shifts in stage II if needed
- Concern is for allowance to deviate
- May want to use more conservative approach

Future directions

- More conservative approach to OK design
- Investigate p-value calculation

Acknowledgements

My deepest appreciation goes to:

- Advisor: Tatsuki Koyama
- DGS and committee member: Jeffrey Blume
- My family
- Faculty
- Fellow graduate students