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

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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 $H_0 : p_0 \leq 0.25$, $H_1 : p_1 > 0.4$, $\alpha = 0.05$, $\beta = 0.2$

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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 hypothesis testing
- 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

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