Sample size re-estimation incorporating prior information on a nuisance parameter

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Agenda

Sample size planning in clinical trials
Incorporating prior information into the sample size planning
Sample size re-estimation
Incorporating prior information into the sample size re-estimation
Discussion and outlook
Sample size planning in a clinical trial

- From a statistical perspective, sample size of a clinical trial is affected by multiple parameters
  - Type I error rate \( \alpha \)
  - Target power \( 1 - \beta \)
  - Target effect size: \( \delta^* \)
  - Outcome variance: \( \sigma^2 \)
- Type I error rate is usually chosen as \( \alpha = 2.5\% \) (one-sided)
- Target power usually a value \( \geq 80\% \)
- Target effect size often determined by what is clinically relevant
- Making assumptions about the outcome variance \( \sigma^2 \) is often a key issue
  - Where to get information on variance from?
  - How to (formally) use historical information on the variance in the sample size planning?
Clinical trial setting

- Two-arm parallel group superiority trials with normally distributed endpoints planned and analyzed using frequentist methods
- $X_{ij} | \mu_i, \sigma^2 \sim N(\mu_i, \sigma^2); \quad j = 1, \ldots, n; \quad i = T, C$
- Hypothesis of interest: $H_0: \mu_T \leq \mu_C$ vs $H_1: \mu_T > \mu_C$
- Analysis method: two-sample Student’s t-test with test statistic $T = \sqrt{\frac{n}{2}} \frac{\bar{X}_T - \bar{X}_C}{\hat{\sigma}}$
- (Approximate) sample size required for a power of $1 - \beta$:
  $$n = 2 \frac{(q_{1-\alpha} + q_{1-\beta})^2}{\delta^2} \sigma^2$$
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Incorporating prior information into the sample size re-estimation

Discussion and outlook
Summarizing prior information on $\sigma^2$

- **Goal**: Summarize prior information on variance through a random effects meta-analysis using a Bayesian hierarchical model (Schmidli et al, 2017)
- **Meta-analytic-predictive (MAP) approach**: Use hierarchical model to account for between-trial heterogeneity in order to derive an informative prior from historical data
- Posterior predictive distribution for the variance of a new clinical trial is the MAP prior
- Information about $j = 1, ..., J$ historical clinical trials
  - Sample variance: $s_j^2$
  - Degrees of freedom: $\nu_j$
- (Unknown) true variance: $\sigma_j^2$
Summarizing prior information on $\sigma^2$

- Model for determining posterior predictive distribution of $\sigma^2$:
  
  $s_j^2 | \sigma_j^2 \sim \text{Gamma} \left( \frac{\nu_j}{2}, \frac{\nu_j}{2\sigma_j^2} \right)$
  
  $\log(\sigma^2), \log(\sigma_1^2), ..., \log(\sigma_J^2) | \mu, \tau \sim \mathcal{N}(\mu, \tau^2)$

- Use noninformative or weakly informative prior for $\mu$

- Use Half-normal prior for between-study variability: $\tau \sim \text{HN} \left( sd = \frac{\sqrt{2}}{2} \right)$ or $\tau \sim \text{HN} \left( sd = \frac{\sqrt{2}}{4} \right)$

| Heterogeneity  | Small  | Moderate | Substantial | Large  | Very Large |
|----------------|--------|----------|-------------|--------|------------|
| $\tau$         | 0.09   | 0.18     | 0.35        | 0.7    | 1.4        |

95% PI for $\sigma^2$:

- Small: [0.84, 1.19]
- Moderate: [0.7, 1.42]
- Substantial: [0.5, 1.99]
- Large: [0.25, 3.94]
- Very Large: [0.06, 15.55]

$\mu = \log(1)$. Table taken from Schmidli et al.
Prior information on $\sigma^2$ and sample size planning

- Various approaches for possible
- Bayes estimator of $\sigma^2$ can be plugged into the sample size formula
  - Natural choices are prior mean or prior median
  - Uncertainty of the prior information of $\sigma^2$ is not considered
- To consider the variability of the prior, the sample size can be planned either based on quantiles of the prior or based on the unconditional power
- Unconditional power $B(n, \delta, \alpha, \beta) = \int P(T > t_{1-\alpha} | n, \delta, \sigma, \alpha, \beta) \cdot f_{\sigma^2}(x)dx$
Clinical trial in hypertension

Trial setting

- Aim is to plan the sample size of a clinical trial assessing the efficacy of an intervention for blood pressure control
  - Population: Patients with hypertension
  - Treatment: Experimental intervention vs standard of care
  - Endpoint: Change in systolic blood pressure between baseline and timepoint $T$

- Assumed parameters for sample size calculation
  - Effect size: $\delta = -6.3$ mmHg
  - One-sided significance level: $\alpha = 0.025$
  - Target power: 90%

- Glynn et al. published a meta-analysis that includes reported sample variances
Clinical trial in hypertension
Summary of historical sample variances
Clinical trial in hypertension

MAP prior for $\sigma^2$

| Statistic          | Value |
|--------------------|-------|
| 10% Percentile     | 201   |
| 25% Percentile     | 215   |
| Mean               | 250   |
| Median             | 243   |
| 75% Percentile     | 276   |
| 90% Percentile     | 318   |
| ESS                | 41    |

Black line: $0.35 \cdot \text{InvGamma}(12.2,2813.6) + 0.65 \cdot \text{InvGamma}(42.9,10467.6)$
Clinical trial in hypertension

Effect of variance $\sigma^2$ on sample size

- Effect size: $\delta = -6.3$ mmHg
- Significance level: $\alpha = 0.025$
- Target power: 90%

| Statistic        | $\sigma^2$ | Total sample size |
|------------------|------------|-------------------|
| 10% Percentile   | 201        | 160               |
| 25% Percentile   | 215        | 172               |
| Mean             | 250        | 200               |
| Median           | 243        | 194               |
| 75% Percentile   | 276        | 220               |
| 90% Percentile   | 318        | 254               |
Clinical trial in hypertension

Power depending on variance $\sigma^2$
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Sample size re-estimation

General considerations

- Trial designs with an internal pilot study can be used to re-estimate the outcome variance and sample size of the ongoing clinical trial (Wittes and Brittain, 1990).
- Sample size re-estimation (SSR) is performed based on the results of the internal pilot study.
  - Here we focus on SSR based on the variance.
- SSR either be done based on blinded or unblinded data.
- Blinded SSR has logistical advantages and allows preserving trial integrity without requirement of further steps.
  - Focus on unblinded sample size re-estimation first in this presentation.
    - Extension to blinded sample size re-estimation is discussed later.
Sample size re-estimation
Step-by-step approach

1. Calculate initial sample size $N_0$
   - Based on estimates of the outcome variance from previous studies

2. Review sample size
   - Performed when $p \cdot N_0$ (e.g., $p = 0.5$) patients have completed the study
   - Re-estimation of sample size based on sample variance from $p \cdot N_0$ patients

3. Recruit remaining patients

4. Conduct final analysis
   - Analysis based on all patients
Sample size re-estimation

Illustration

SSR: $N_{\text{new}} = 20$
Sample size re-estimation without prior information

- Estimate variance and plug estimate into the same sample size formula
- Unblinded SSR: Variance is estimated using pooled sample variance
- Blinded SSR: Variance is estimated using one-sample variance estimator
  - One-sample variance estimator: Sample variance ignore treatment group
  - Generally, maintains type I error rate control
- For more information: Friede and Kieser (2013)
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Sample size re-estimation
Incorporating prior information

- Idea for incorporating prior information into the sample size re-estimation
  - Update MAP prior for $\sigma^2$ with data from the internal pilot study
  - Re-estimate sample based on posterior distribution for $\sigma^2$

- Assume that prior (and thus posterior) for $(\mu_T, \mu_C)$ and $\sigma^2$ are independent
- Assume that prior $p_{\sigma^2}(\cdot)$ is a mixture inverse-Gamma distribution
- Posterior distribution of $\sigma^2$ is a mixture of inverse-Gamma distributions

$$\sigma^2 | s_{SSR}^2 \sim \sum_l w_l^* \text{InvGamma} \left( a_l + \frac{n_1 - 2}{2}, b_l + \frac{n_1 - 2}{2} s_{SSR}^2 \right)$$

- Closed form expression for updated weights $w_l^*$ (see Mütze et al)
Clinical trial in hypertension

SSR incorporating prior information

Prior for \( \sigma^2 \):
\[ 0.35 \cdot \text{InvGamma}(12.2, 2813.6) + 0.65 \cdot \text{InvGamma}(42.9, 10467.6) \]

Assumed effect: \( \delta = -6.3 \)
Operating characteristics
Simulation study setup

- Comparison of two sample size re-estimation approaches
  - based on unblinded sample variance $s^2$ (frequentist)
  - posterior mean (Bayesian)
- Operating characteristics of interest
  - Power
  - Variability of final sample size
- Sample size of fixed design trial: 128

### Parameter Value

| Parameter                        | Value       |
|----------------------------------|-------------|
| Significance level               | 0.025       |
| Target power                     | 0.8         |
| Treatment effect $\delta$        | 0.5         |
| True variance $\sigma^2$         | 1           |
| IPS size $n_1$                   | 10, 20, ..., 100 |
| Expected value of prior $p_{\sigma^2}(\cdot)$ (no prior-data conflict) | 1           |
| Expected value of prior $p_{\sigma^2}(\cdot)$ (prior-data conflict) | 0.49       |
| Effective sample size ESS of $p_{\sigma^2}(\cdot)$ | 6, 25, 50 |
Power of SSR procedures
No prior data conflict
Final sample size of SSR procedures

No prior-data conflict

ESS = 6

ESS = 25

ESS = 50

10/50/90 perc. of final sample size

Internal pilot study sample size $n_1$

Prior information

No prior information
Power of SSR procedures

Prior-data conflict
Robustifying the prior

- **Idea**: Mitigate the risk of a prior-data conflict by robustifying the prior (Schmidli et al., 2014)
- Robustified MAP prior $p_{rMAP}(\cdot)$ is the mixture distribution of the MAP prior and the vague conjugate prior with mixture probability $w_R$

\[
p_{rMAP}(x) = w_R \cdot p_V(x) + (1 - w_R) \cdot p_{MAP}(x)
\]
- Prior probability $w_R$ of a prior-data conflict reflects the initial information of how likely a prior-data conflict is
- In the following vague prior is an $InvGamma(2,1)$ distribution
Power of SSR procedures
Prior-data conflict: Robustified prior and $n_{IPS} = 60$
Extension to blinded data

- Various approaches for updating the variance prior based on blinded information:
  - blinded one-sample variance estimator
  - model the data of the internal pilot study as a mixture of two normal distributions
  - randomized block design: update prior information based on distribution of block sums (Xing and Ganju, 2005)
- All methods face same issue concerning prior-data conflict
  - Internal pilot study too small to dominate prior and thereby resolve prior-data conflict
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- Incorporating prior information into sample size re-estimation
  - Reduces variability of re-estimated sample size
  - Bears risk of under- or overpowered clinical trials in the case of prior-data conflict

- Extension to blinded data: methods face same issue concerning prior-data conflict as re-estimation based on unblinded data

- Other methods for selecting final sample size such as decision theoretic approaches (Stallard, 1998)

- GitHub repository: https://github.com/tobiasmuetze/varmap

- Future research
  - Extension to non-normally distributed endpoints
  - Incorporating prior information into effect-based sample size re-estimation
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Thank you