Blinded sample size re-estimation accounting for uncertainty in small sample mid-trial estimation

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Background

◆ **Sample size estimation**

✓ In randomized clinical trial, it is important to set the target sample size accurately at the design stage **to ensure the target power**.

Notation & Setting

- Consider a randomized trial comparing two groups' mean with continuous values as the endpoint.
  - $Z \in \{0,1\}$: treatment index (1: 1 allocation)
  - $Y_{z,i} \overset{i.i.d.}{\sim} N(\mu_z, \sigma^2)$: distribution of outcomes in group z
  - $\Delta := \mu_1 - \mu_0$: true treatment effect
  - δ: target treatment effect
- Final analysis: the one-sided t-test

$H_0: \Delta = 0 \quad vs. \quad H_1: \Delta = \delta\ (> 0)$

$T = (\bar{Y}_1 - \bar{Y}_0)/\sqrt{2\hat{\sigma}^2/n}$ ($\bar{Y}_z$: sample mean, $\hat{\sigma}^2$: unbiased variance)

α: one-sided significance level $1-\beta$: target power

$$Power \approx 1 - \Phi\left(z_\alpha - \delta \cdot \sqrt{\frac{n}{2\sigma^2}}\right) \Rightarrow n \approx 2\left(\frac{z_\alpha - z_{1-\beta}}{\delta}\right)^2 \sigma^2$$

z_α: the upper $100 \cdot \alpha\%$ quantile of $N(0,1)$ n: sample size per group

✓ To calculate the sample size, it is necessary to specify σ^2.

✓ The misspecification of σ^2 can lead to underpowered studies.

✓ It is difficult to set σ^2 correctly at the design stage.

◆ **Blinded sample size re-estimation**

- Consider re-estimating sample size after observing n_{int} subjects per group
- To keep integrity, it is preferable **to conceal allocation information Z.**



One-Sample variance (Gould and Shih, 1992)

$$\hat{\sigma}^2_{OS} = \frac{1}{2n_{int}-1}\sum_{z=0}^{1}\sum_{i=1}^{n_{int}}\left(Y_{z,i} - \bar{Y}_{int}\right)^2 \quad \left(\bar{Y}_{int} = \frac{1}{2n_{int}}\sum_{z=0}^{1}\sum_{i=1}^{n_{int}} Y_{z,i}\right)$$

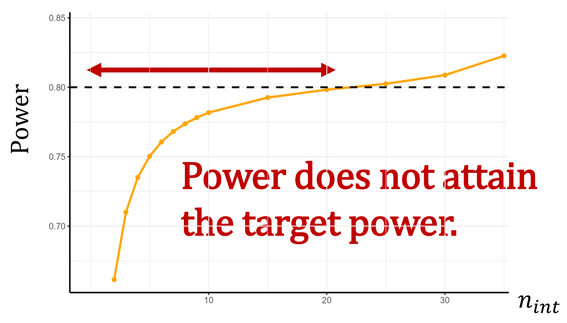
Existing problem

Example:

$\alpha = 0.025, 1-\beta = 0.8$

$\Delta = \delta = 1, \sigma = 1.5$

····· : target power



✓ If n_{int} is small, $\hat{\sigma}^2_{OS}$ may lead to underpowered final analyses.

Idea

- We propose a method to control the margin with $100 \cdot (1-\gamma)\%$ upper confidence limit for σ^2 tractable with blinded internal pilot study.

⇒ How can we determine $1-\gamma$ to attain the target power?

✓ **We use relationships between central and non-central chi-squared distributions.**

Notation for central and non-central χ^2 distribution

Degree of freedom: $2n_{int}-1$ Non-centrality parameter: λ

Distribution	Random variable	Probability density function	Upper $100 \cdot (1-\gamma)\%$ quantile
$\chi^2_{2n_{int}-1}$	W	f_W	$d_{1-\gamma}$
$\chi^2_{2n_{int}-1,\lambda}$	W_λ	f_{W_λ}	$d_{\lambda,1-\gamma}$

Asymptotically valid but infeasible upper confidence limit approach

$100 \cdot (1-\gamma)\%$ upper confidence limit for σ^2:

$$\hat{\sigma}^2_{U,1-\gamma} = \hat{\sigma}^2_{OS} \cdot \frac{2n_{int}-1}{d_{\lambda,1-\gamma}} \quad \left(\lambda = \left(\frac{\Delta}{\sigma}\right)^2 \cdot \frac{n_{int}}{2}\text{: unknown}\right)$$

Consider sample size re-estimation: $\hat{n}_{fin} = 2\left(\frac{z_\alpha - z_{1-\beta}}{\delta}\right)^2 \hat{\sigma}^2_{U,1-\gamma}$

Asymptotic conditional power function given $\hat{n}_{fin}$ (Zucker et al. 1999):

$$P\left(T \geq t_{2\hat{n}_{fin}-2} \middle| \Delta = \delta, \hat{n}_{fin}\right) \approx 1 - \Phi\left(z_\alpha - \delta \cdot \sqrt{\frac{\hat{n}_{fin}}{2\sigma^2}}\right)$$

$$= 1 - \Phi\left(z_\alpha - \left|z_\alpha - z_{1-\beta}\right| \cdot \sqrt{\frac{\hat{\sigma}^2_{U,1-\gamma}}{\sigma^2}}\right)$$

From $\hat{\sigma}^2_{U,1-\gamma}/\sigma^2 = W_\lambda/d_{\lambda,1-\gamma}$, power is expressed as following;

$$P\left(T \geq t_{2\hat{n}_{fin}-2} \middle| \Delta = \delta\right) \approx 1 - \int_0^\infty \Phi\left(z_\alpha - \left|z_\alpha - z_{1-\beta}\right| \cdot \sqrt{\frac{w}{d_{\lambda,1-\gamma}}}\right) f_{W_\lambda}(w)dw$$

※ Since λ includes the unknown effect size Δ/σ, it is not possible to estimate and calculate $\hat{\sigma}^2_{U,1-\gamma}$ and power.

Proposed method: Use of a conservative upper confidence limit for σ^2 estimable in a blinded review

$100 \cdot (1-\gamma)\%$ conservative upper confidence limit for σ^2:

$$\bar{\sigma}^2_{U,1-\gamma} = \hat{\sigma}^2_{OS} \cdot \frac{2n_{int}-1}{d_{1-\gamma}} \quad (\geq \hat{\sigma}^2_{U,1-\gamma}$$ ☜ Infeasible upper confidence limit)

Consider sample size re-estimation: $\hat{n}_{fin} = 2\left(\frac{z_\alpha - z_{1-\beta}}{\delta}\right)^2 \bar{\sigma}^2_{U,1-\gamma}$

From $\bar{\sigma}^2_{U,1-\gamma}/\sigma^2 = W_\lambda/d_{1-\gamma}$, power is expressed as following;

$$P\left(T \geq t_{2\hat{n}_{fin}-2} \middle| \Delta = \delta\right) \approx 1 - \int_0^\infty \Phi\left(z_\alpha - \left|z_\alpha - z_{1-\beta}\right| \cdot \sqrt{\frac{w}{d_{1-\gamma}}}\right) f_{W_\lambda}(w)dw \quad -①$$

From the fact (Lehmann 1955; Finner and Roters 1997),

$$1 - \int_0^\infty g(w) f_{W_\lambda}(w)dw \geq 1 - \int_0^\infty g(w) f_W(w)dw \quad (g\text{: non-increasing}),$$

$$① \geq 1 - \int_0^\infty \Phi\left(z_\alpha - \left|z_\alpha - z_{1-\beta}\right| \cdot \sqrt{\frac{w}{d_{1-\gamma}}}\right) f_W(w)dw \quad (W \sim \chi^2_{2n_{int}-1}) \quad -②$$

This lower bound can be calculated given only n_{int} and $1-\gamma$.

Proposed method's procedure

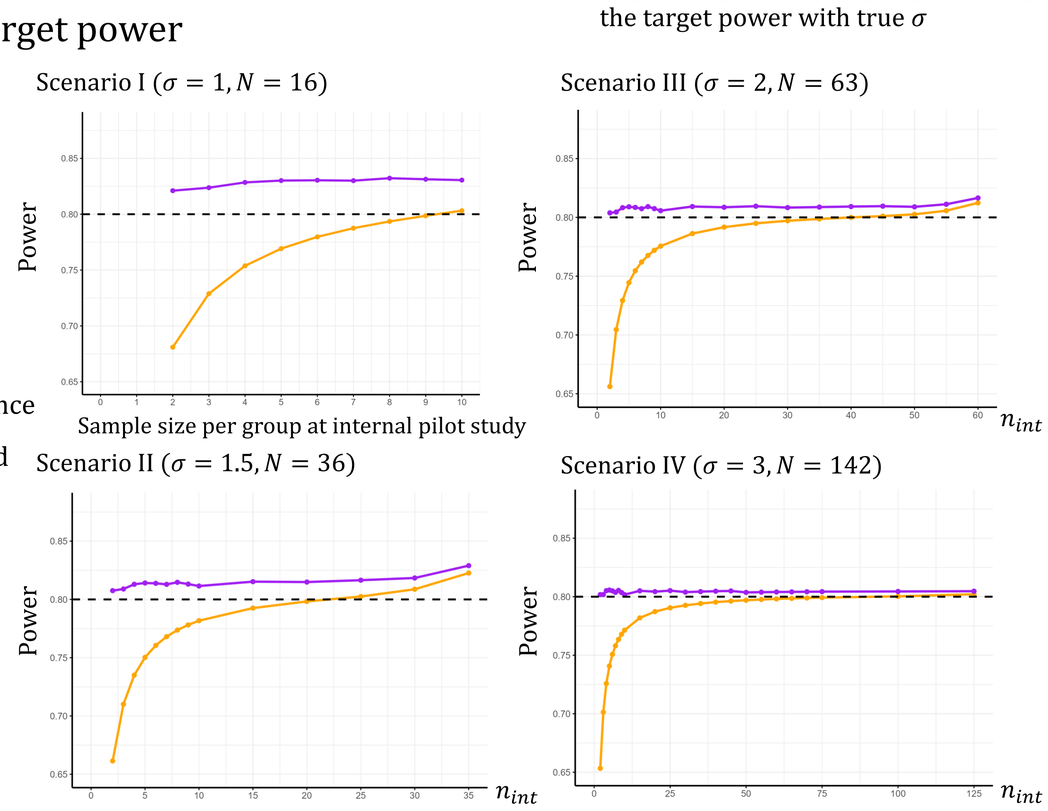
1. **Design stage** Set $\alpha, 1-\beta, \delta$ and n_{int}.
2. **Design stage** Determine $1-\gamma$ that satisfies ② $= 1-\beta$.
3. **Interim analysis** Calculate $\bar{\sigma}^2_{U,1-\gamma}$ and $\hat{n}_{fin} = 2\left(\frac{z_\alpha - z_{1-\beta}}{\delta}\right)^2 \bar{\sigma}^2_{U,1-\gamma}$.
4. **Final analysis** Carry out the final analysis with $\hat{n}_{fin}$ subjects.

Numerical study

$\alpha = 0.025, 1-\beta = 0.80, \Delta = \delta = 1$

▬▬ : target power

N: Target sample size per group attaining the target power with true σ



Conclusion

✓ Existing method leads to underpowered studies with small blinded reviews.

✓ We consider a conservative upper confidence limit estimable in a blind review and realize a refined method to overcome the above issue.

<References>

[1] Finner, H. and Roters, M. (1997). Log-concavity and inequalities for chi-square, f and beta distributions with applications in multiple comparisons. *Statistica Sinica*, 7(3): 771-787.

[2] Gould, A. L. and Shih, W. J. (1992). Sample size re-estimation without unblinding for normally distributed outcomes with unknown variance. *Communications in Statistics-Theory and Methods*, 21(10):2833–2853.

[3] Lehmann, E. L. (1955). Ordered families of distributions. *In Slected Works of EL Lehmann*, pages 757-777. Springer