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Sample Size Re-estimation for Non-inferiority Trials

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Non-inferiority Trials

- It is unethical to assign participants into a placebo when standard treatment exists
- Superiority trials can evaluate improvement in efficacy of a new treatment
- Non-inferiority trials assess whether a new treatment is “not worse” to the existing treatment

(Mauri and D'Agostino 2017)

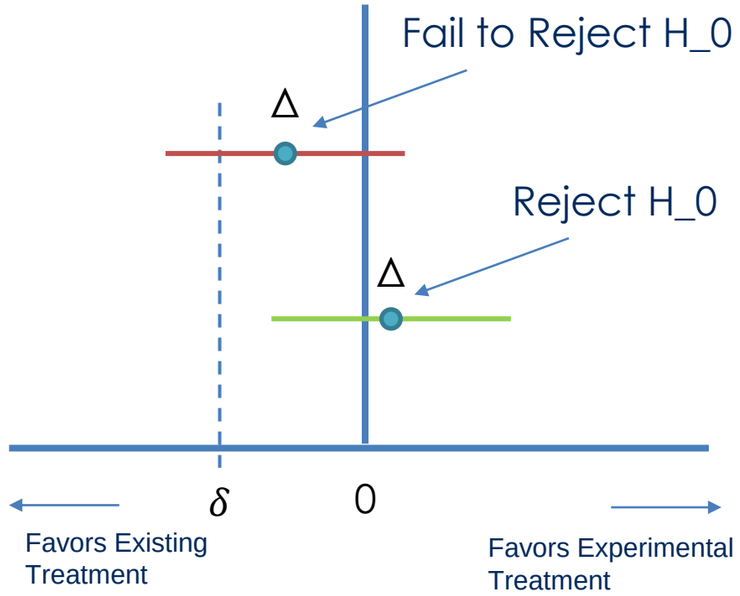
Hypothesis

- Δ = mean effect of treatment arm – mean effect in control arm
- δ = non-inferiority margin (NIM), a clinically significant value

$$H_0 : \Delta \leq \delta$$

$$H_a : \Delta > \delta$$

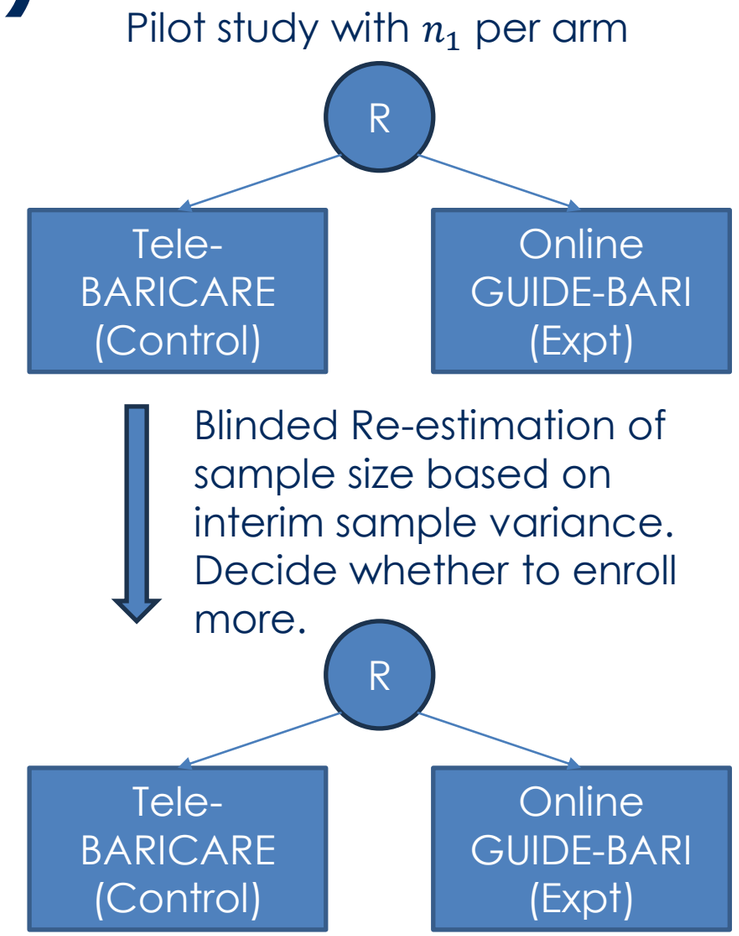
(Friede 2003, Lu 2016)



Motivation of Re-estimation from GUIDE-BARI Trial (PIs: Sockalingam, Cassin & Agic)

- Patients may regain weight 12 - 24 months post-bariatric surgery – leads to mental distress.
- Compare online GUIDE-BARI vs Tele-BARICARE intervention based on the Binge Eating Scale (BES).
- σ unknown, mis-specified σ would cause the study to be underpowered.
- Start with an internal pilot study and re-estimate sample size based on interim sample variance.

(Sockalingam, Leung et al. 2023)



Blinded Sample Size Re-estimation

Blinded: not knowing treatment assignment at interim level

$$N = \frac{2(z_{1-\alpha} + z_{1-\beta})^2 \sigma^2}{(\Delta^* - \delta_1)^2}$$

Conventional sample size estimation

$$S^2_{1,os} = \frac{1}{2n_1 - 1} \sum_{j=1}^{2} \sum_{k=1}^{n_1} (X_{1jk} - \bar{X}_{1..})^2$$

Overall sample variance at stage 1

$$\hat{N}_{recalc} = \frac{2(z_{1-\alpha} + z_{1-\beta})^2 S^2_{1,os}}{(\Delta^* - \delta_1)^2}$$

Re-estimate sample size based on updated variance estimation

$$n = \max(\lceil \hat{N}_{recalc} \rceil, n_1)$$

We either stop at stage 1 or enroll more patients based on the re-estimation

(Friede 2003, Lu 2016)

Testing

When stage1 sample size is enough:

$$T = \sqrt{\frac{n_1}{2}}\frac{\bar{X}_{11} - \bar{X}_{12} - \delta_1}{S_{1,\text{pool}}}$$

H0 is rejected if $T \geq t_{1-\alpha,2n_1-2}$

(Friede 2003, Lu 2016)

or we need to enroll more patients:

$$T = \sqrt{\frac{n}{2}}\frac{\bar{X}_1 - \bar{X}_2 - \delta_1}{S_{\text{pool}}}$$

H0 is rejected if $T \geq t_{1-\alpha,2n-2}$

Knowledge Gap

- Existing methods assumes NIM stays constant, but in real world clinicians may alter it after interim results was observed
- To avoid exceeding the maximum allowable sample size
- Changing NIM at stage 1 may affect trial-wide type 1 error rate (T1E)

Study Objectives

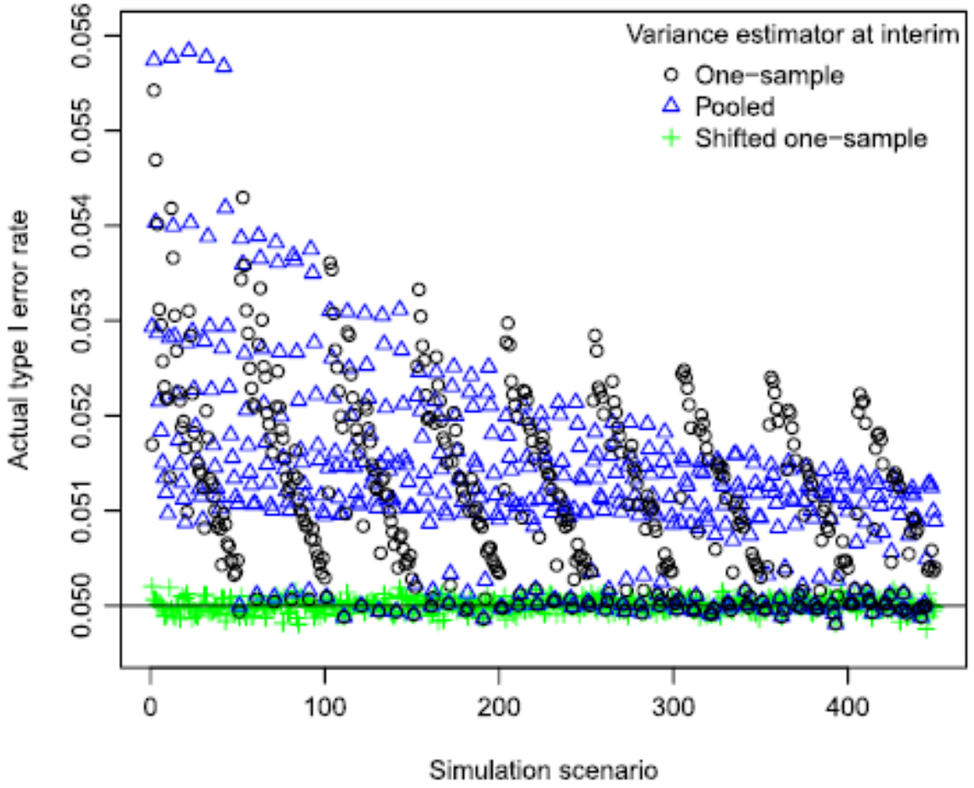
1. To replicate examples provided in the (Lu 2016) using the blindrecalc R package (Baumann 2022)

2. To study the relationship between non-inferiority margin and T1E using simulations from (Lu 2016)

3. To apply this method to the GUIDE-BARI trial at CAMH

Methods

- Obj 1. Re-generate some points from Figure 2 of Lu 2016.
- Obj 2.
  - Fixed inputs are α, β, & σ.
  - Change initial sample size(n1) & Δ* by increment
  - Capture sample size (n) after re-estimation, & actual rejection probability based on the simulation
- Obj 3.
  - Re-estimate sample size with interim sample variance based on different NIM.



(Lu 2016)

References

1. Mauri, L. and R. B. D'Agostino, Sr. (2017). "Challenges in the Design and Interpretation of Noninferiority Trials." N Engl J Med **377**(14): 1357-1367.

2. Friede, T. and M. Kieser (2003). "Blinded sample size reassessment in non-inferiority and equivalence trials." Stat Med **22**(6): 995-1007.

3. Lu, K. (2016). "Distribution of the two-sample t-test statistic following blinded sample size re-estimation." Pharm Stat **15**(3): 208-215.

4. Baumann, L., et al. (2022). "blindrecalc - An R Package for Blinded Sample Size Recalculation." The R Journal **14**(1): 137--145.

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Thank You!

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Possible Extensions (Supplementary)

Computing perspective:

- Current T1E estimation in blindrecalc(Baumann, 2022) R package is MC simulation based, we could try to improve the accuracy while not compromising on the running time

Methodology perspective:

- Develop methods to account for T1E inflation after sample-size re-estimation
- Use Bayesian approach to estimate variance at stage 1

About CAMH research (Supplementary)

- $60.16M of new research grants were awarded (2021-22)
- 1005 peer-reviewed papers published (2022)
- 23 research chairs
- 2020 global research collaborations in 132 countries
- Canada's top mental health research hospital

Source: Annual Report 2022-23 (https://www.camh.ca/en/driving-change/about-camh/performance-and-accountability/annual-report-and-financial-statements/annual-report-2022-2023)