



MRC
Biostatistics
Unit



UNIVERSITY OF
CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 5: Sample Size Re-estimation

Sofía S. Villar

MRC Biostatistics Unit

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Motivating Example

Trial: NOTACS trial (ISRCTN: 14092678)

Goal: Determine if prophylactic use of high flow nasal therapy increases days at home after bypass surgery

Challenge: Sample size calculated based on single center pilot data using a different endpoint

Solution: Sample size reassessment (=sample size review=sample size reestimation)

A general approach to sample size reviews

- Many sample size formulae depend on nuisance parameters, the values of which have to be guessed
- Part way through the trial we will have plenty of data on which to base a better guess
- So, do that, and recalculate the sample size
- Now use the new sample size, perhaps within the limits of minimum and maximum possible values
- Assess the effect of this procedure on type I error: usually it is very small

Sample size review for binary data

Treatments:	Experimental (E) and Control (C)
Success probabilities:	p_E and p_C
Hypotheses:	$H_0 : p_E = p_C$ $H_1 : p_E > p_C$
Type I error:	α (one-sided)
Power:	$1 - \beta$, when $p_E = p_{ER}$ and $p_C = p_{CR}$
Sample sizes:	n_E and n_C , where $n_E + n_C = n$
Allocation ratio:	(1:1), that is $n_E = n_C$

p_{CR} is the anticipated value of p_C , and an improvement from that value to $p_E = p_{ER}$ on E would be clinically worthwhile

Probability difference approach

Initial sample size calculation

Put $\theta = p_E - p_C$, and set power at $\theta = \theta_R = p_{ER} - p_{CR}$

Two popular formulae for n are:

$$n = 2 \left(\frac{z_{1-\alpha} \sqrt{2\bar{p}(1-\bar{p})} + z_{1-\beta} \sqrt{p_{ER}(1-p_{ER}) + p_{CR}(1-p_{CR})}}{\theta_R} \right)^2 \quad (1)$$

(Machin et al., 1997)

and

$$n = 4\bar{p}(1-\bar{p}) \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\theta_R} \right)^2 \quad (2)$$

where $\bar{p} = \frac{1}{2}(p_{ER} + p_{CR})$

To use these formulae:

- use previous data and experience to guess p_{CR}
- consider what difference θ_R would be clinically important
- deduce p_{ER} and \bar{p}

Using these values, find the required sample size n

Then, when data from about $\frac{1}{2}n$ patients are available, a sample size review can be conducted

At the sample size review we do not change θ_R :

- this remains the clinically important difference

To recompute n based on (1), identify the control patients and find an estimate, \hat{p}_C , of p_C as the success rate on C so far

Replace p_{CR} by \hat{p}_C , p_{ER} by $\hat{p}_C + \theta_R$ and $\bar{p} = \hat{p}_C + \frac{1}{2}\theta_R$

To recompute n based on (2), we do not need break the blinding: just estimate \bar{p} as the overall success rate in the trial as a whole (over E and C)

The preservation of blindness makes the second option more attractive

Importance of blinding and allocation concealment

- Eliminates selection bias (who enters the trial in the first place)
- Removes/eliminates performance and ascertainment bias (how the outcome is perceived)

Log-odds ratio approach

Initial sample size calculation

Put

$$\theta = \log \left(\frac{p_E(1 - p_C)}{p_C(1 - p_E)} \right) = \log \left(\frac{p_E}{1 - p_E} \right) - \log \left(\frac{p_C}{1 - p_C} \right)$$

and set power at $\theta = \theta_R$ computed from the values p_{ER} and p_{CR}
The resulting sample size formula is:

$$n = \frac{4}{\bar{p}(1 - \bar{p})} \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\theta_R} \right) \quad (3)$$

This formula can be updated at a sample size review in the same way as equation (2), without breaking the blind

Example

$$\alpha = 0.025, 1 - \beta = 0.90, z_{1-\alpha} = 1.96, z_{1-\beta} = 1.282$$

$$p_{CR} = 0.3, p_{ER} = 0.5, \bar{p} = 0.4$$

Equation (1) - prob diff: $\theta_R = 0.2 \Rightarrow n = 248$

Equation (2) - prob diff: $\theta_R = 0.2 \Rightarrow n = 252$

Equation (3) - log-odds ratio: $\theta_R = 0.847 \Rightarrow n = 244$

Example

After 120 observations, the sample size is reviewed

We find that $\bar{p} = 0.2$, rather than 0.4

Retaining probability difference: $\theta_R = 0.2$, Equation (2) $\Rightarrow n = 168$

- sample size goes down
- $\theta_R = 0.2$ consistent with $p_{CR} = 0.1$, $p_{ER} = 0.3$

Retaining log-odds ratio: $\theta_R = 0.847$, Equation (3) $\Rightarrow n = 366$

- sample size goes up
- $\theta_R = 0.847$ consistent with $p_{CR} = 0.134$, $p_{ER} = 0.266$

Normally distributed data

- Treatments: Experimental (E) and Control (C)
Distributions: $N(\mu_E, \sigma^2)$ and $N(\mu_C, \sigma^2)$
Hypotheses: $H_0 : \mu_E = \mu_C$ $H_1 : \mu_E > \mu_C$
Type I error: α (one-sided)
Power: $1 - \beta$, when $\mu_E = \mu_{ER}$ and $\mu_C = \mu_{CR}$
Sample sizes: n_E and n_C , where $n_E + n_C = n$
Allocation ratio: (1:1), that is $n_E = n_C$

Put $\theta = \mu_E - \mu_C$ and $\theta_R = \mu_{ER} - \mu_{CR}$

Let σ_R^2 denote the anticipated common variance

The sample size is given by

$$n = 4\sigma_R^2 \left(\frac{z_{1-\alpha} + z_{1-\beta}}{\theta_R} \right)^2 \quad (4)$$

The actual values of μ_{ER} and μ_{CR} have no effect on n other than through θ_R

The anticipated variance σ_R^2 is very influential, and is replaced by an estimate at the sample size review

Estimating σ^2

a) Use the conventional unbiased estimate

$$\hat{\sigma}^2 = s^2 = \frac{\sum_{h=1}^{n_E} (x_{hE} - \bar{x}_E)^2 + \sum_{h=1}^{n_C} (x_{hC} - \bar{x}_C)^2}{n - 2} \quad (5)$$

based on the n observations available so far

To use this requires breaking the blind, at least as far as separating the two treatment groups: their identities need not be revealed

Estimating σ^2

b) Avoid unblinding, using a simple adjustment (Gould, 1995)
For each term in (5)

$$\sum_{h=1}^{n_E} (x_{hE} - \bar{x}_E)^2 = \sum_{h=1}^{n_E} (x_{hE} - \bar{x} + \bar{x} - \bar{x}_E)^2 = \sum_{h=1}^{n_E} (x_{hE} - \bar{x})^2 - n_E (\bar{x} - \bar{x}_E)^2$$

Substitute in equation (5)

$$\sum_{h=1}^{n_E} (x_{hE} - \bar{x}_E)^2 + \sum_{h=1}^{n_C} (x_{hC} - \bar{x}_C)^2 = \sum_{j=E,C} \sum_{h=1}^{n_j} (x_{hj} - \bar{x})^2 - \frac{n_C n_E}{n} (\bar{x}_C - \bar{x}_E)^2$$

If desired difference is present: $(\bar{x}_E - \bar{x}_C) = \theta_R$

$$\sum_{h=1}^{n_E} (x_{hE} - \bar{x}_E)^2 + \sum_{h=1}^{n_C} (x_{hC} - \bar{x}_C)^2 = \sum_{j=E,C} \sum_{h=1}^{n_j} (x_{hj} - \bar{x})^2 - \frac{n_C n_E}{n} \theta_R^2$$

Can use estimate $\tilde{\sigma}^2$ for sample size review without unblinding

$$\tilde{\sigma}^2 = \frac{\sum_{j=E,C} \sum_{h=1}^{n_j} (x_{hj} - \bar{x})^2}{n-2} = \frac{(n-1)\tilde{\sigma}_T^2 - \frac{n_E n_C}{n} \theta_R^2}{n-2} \quad (6)$$

$\tilde{\sigma}_T^2$: The estimate of total variance

Example

$$\alpha = 0.025, 1 - \beta = 0.90, z_{1-\alpha} = 1.96, z_{1-\beta} = 1.282$$
$$\theta_R = 0.5, \sigma_R = 1.0$$

Equation (4) $\Rightarrow n = 168$

After 80 patients:

$$n_E = 40, \bar{x}_E = 5.6, s_E = 1.45 \quad n_C = 40, \bar{x}_E = 5.3, s_E = 1.26$$

$$\tilde{\sigma}_T^2 = 1.844$$

Unblinded approach

$$\begin{aligned}\text{Equation (5)} \quad (n - 2)\hat{\sigma}^2 &= (n_E - 1)s^2_e + (n_C - 1)s^2_C \\ &= 143.91\end{aligned}$$

So that

$$\hat{\sigma}^2 = 1.845$$

From Equation (4) the new sample size is $n = 310$.

Blinded approach

$$\text{Equation (6)} \quad \tilde{\sigma}^2 = \frac{145.7139 - \frac{80}{4}0.5^2}{78} \\ = 1.804$$

From Equation (4) the new sample size is $n = 304$.

Discussion

- Sample size reestimation is an adaptive design with a single interim analysis which may lead to a reassessment of sample size
- Its use is becoming widespread
- Regulatory authorities are generally well-disposed towards it
- Using an E-M algorithm (Gould and Shih, 1992; Gould, 1995) should not be used ⇒ See Friede and Kieser (2002)

