MRC Biostatistics Unit

UNIVERSITY OF CAMBRIDGE

Adaptive Methods in Clinical Research

Lecture 7: Sample Size Re-estimation

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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:	$H_0 : p_E = p_C$ $\quad$ $H_1 : p_E > p_C$
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

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)

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:

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

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 $\hat{p} = 0.2$, 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:	$H_0 : \mu_E = \mu_C \quad H_1 : \mu_E > \mu_C$
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

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

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

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

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

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

$\tilde{\sigma}_T^2$: 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

$$\begin{aligned} \text{Equation (5)} \quad (n-2)\hat{\sigma}^2 &= (n_E - 1)s^2 e + (n_C - 1)s_C^2 \\ &= 143.91 \\ \text{So that} & \\ \hat{\sigma}^2 &= 1.845 \end{aligned}$$

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

Blinded approach

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

$$0 \quad 1.804$$

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 $\Rightarrow$ See Friede and Kieser (2002)