GSD with unequally sized stages

Werner Brannath

VO ”Sequential and Adaptive Designs”,
University Bremen

Introduction

- Assume that we have planned the GSD with equally spaced stages, but the stage-wise sample sizes n_k are unequal.
- Since the anticipated type I and II error rates depend on the sample size ratios, they may not be reached; see Table 3.1 in WaBr16.
- Typically, only small deviations from the preplanned α and β
- For extreme cases, the type I error inflation may be relevant.
- From a theoretical (and practical) point of view, deviations are unsatisfactory.

GSD with pre-planned unequal n_k

- We have $\text{Cor}(Z_j^*, Z_k^*) = \sqrt{\min(t_j, t_k)/\max(t_j, t_k)}$ and

$$\mathbf{E}(Z_k^*) = \vartheta_k = \sqrt{t_k}\,\vartheta_K = \sqrt{t_k K}\,\vartheta_1$$

- We can calculate all boundaries (e.g. Pocock or O'Brien & Fleming) also with unequal stages.

- Two possible versions for the Δ-family:

$$\tilde{u}_k = c(K, \alpha, \beta, \Delta) k^{\Delta - 0.5} \quad \text{and} \quad u_k = c(K, \alpha, \beta, \Delta) \left(\frac{t_k}{t_1}\right)^{\Delta - 0.5}$$

- Figure 3.1 in WaBr16: number of stage K varies; first information times omitted; u_k robust with respect to K and hence preferable.
- One can optimize ASN with respect to Δ and information times; see Table 3.3 in WaBr16.

Spending Function Approach

The idea of Lan & DeMets (1983)

- It is usually difficult or even impossible to achieve the pre-planned sample sizes perfectly.
- One reason is that we need to fix a date for the DMC to meet.
- So solve this issue, Lan & DeMets suggest to fix the maximum sample size N and a “spending function at level α”

$$\alpha^*(t), \quad t \in [0, 1]$$

  that is strictly increasing with $\alpha(0) = 0$ and $\alpha(1) = \alpha$.

- Spending function α^* defines how the level is spend in course of the study (in terms of the information time) or over the stages.

Method of Lan & DeMets (1983)

- In the 1st interim analysis (IA) calculate $t_1 = n_1/N$ and u_1, s.th.

$$\mathbf{P}\big(|Z_1^*| \geq u_1\big) = \alpha^*(t_1)$$

- In the 2nd IA we calculate $t_2 = (n_1 + n_2)/N$ and u_2, s.th.

$$\alpha_1^*(t_1) + \mathbf{P}\big(|Z_1^*| < u_1,\ |Z_2^*| \geq u_2\big) = \alpha^*(t_2)$$

- In the kth IA calculate $t_k = (n_1 + \cdots + n_k)/N$ and u_k, s.th.

$$\alpha^*(t_{k-1}) + \mathbf{P}\big(|Z_1^*| < u_1, \ldots, |Z_{k-1}^*| < u_{k-1},\ |Z_k^*| \geq u_k\big) = \alpha^*(t_k)$$

  This means to use the level $\alpha^*(t_k)$ up to stage k.

- In the last stage we use up the full label α, i.e. we choose $t_K = 1$.

Overrunning

- By the definition

$$\tilde{\alpha}^*(t) := \begin{cases} \alpha^*(t) & \text{for } t \in [0,1], \\ \alpha & \text{for } t > 1 \end{cases}$$

  the pre-planned maximum sample size N can be exceeded.

- We stop the study at the first stage k where

$$t_k = (n_1 + \cdots + n_k)/N > 1.$$

  This gives a random last stage K.

- At the last stage K we choose u_K such that

$$\mathbf{P}_0\Big(|Z_1^*| < u_1, \cdots, |Z_{K-1}^*| < u_{K-1},\ |Z_K^*| \geq u_K\Big) = \alpha - \alpha^*(t_{K-1})$$

Underrunning

- We can also stop the study when

$$t_k = \frac{n_1 + \cdots + n_k}{N} < 1$$

- In this case we also choose u_k such that

$$\mathbf{P}_0\Big(|Z_1^*| < u_1, \cdots, |Z_{k-1}^*| < u_{k-1},\ |Z_K^*| \geq u_k\Big) = \alpha - \alpha^*(t_{k-1})$$

- By this, we use neither the spending function α^* nor $\tilde{\alpha}^*$. Instead, we set $\alpha^*(t_k)$ to α.

Important remarks

- u_k is independent of all future u_j for $j > k$ and depends only on the past u_i, $i < k$.
- The α-spending function approach controls the level only if n_K is independent from the data, i.e. from $Z_1^*, \ldots, Z_{k-1}^*$.
- This means that we are not allowed to choose the sample sizes based on the unblinded data.
- We may (and often do) choose the sample size on independent (or blinded) data, like e.g. the recruitment rate.

Examples for spending functions (see Fig. 3.2 in WaBr16)

- To mimic Pocock's design (Lan & DeMets, 1983):

$$\alpha_1^*(t) = \alpha \log \Big(1 + (e-1)t\Big), \quad t \in [0,1]$$

- To mimic the O'Brien & Fleming design (Lan & DeMets, 1983):

$$\alpha_2^*(t) = \begin{cases} 4\Big\{1 - \Phi^{-1}\big[\Phi(1-\alpha/4)/\sqrt{t_k}\big]\Big\} & \text{one-sided} \\ 4\Big\{1 - \Phi^{-1}\big[\Phi(1-\alpha/2)/\sqrt{t_k}\big]\Big\} & \text{two-sided} \end{cases}$$

- Spending function family of Kim & DeMets (1987)

$$\alpha_3^*(\rho, t) = \alpha\, t^\rho, \quad t \in [0,1], \quad \text{for some } \rho > 0$$

- Spending function family of Hwang et al. (1980)

$$\alpha_4^*(\gamma, t) = \begin{cases} \alpha\,(1-e^{-\gamma t})/(1-e^{-\gamma}) & \text{for } \gamma \neq 0 \\ \alpha\, t & \text{for } \gamma = 0 \end{cases}, \quad t \in [0,1]$$