GSD with equally sized stages

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Introduction

- Because with $t_j = N_j/N_K$ we have

$$\mathrm{Cor}(Z_j^*, Z_k^*) = \sqrt{N_j/N_k} = \sqrt{t_j/t_k}, \quad \text{for } j < k,$$

  the type I error depends on the *fraction* of the sample sizes but is independent of its actual size.

- We assume now that: $\qquad n_1 = \cdots = n_K =: n$
- Then $t_k = k/K$ and $\mathrm{Cor}(Z_j, Z_k) = \sqrt{j/k}$ for all $j \leq k \leq K$.

- This is a very common planning assumption,
- which is often not fully realized in practise. However, with small deviations, α is achieved approximately.
- Severe deviations need to be accounted for; see later.

Distributional consequences

$N_k = kn$ and $X_{11}, \ldots, X_{1n}, \ldots, X_{K1}, \ldots, X_{Kn} \sim_{\text{iid}} N(\mu, \sigma^2)$ imply:

- $Z_k^* = \sum_{k=1}^{K} Z_k / \sqrt{k} \quad \sim \quad N(\vartheta_k, 1)$
- $\vartheta_k = \mathbf{E}(Z_k^*) = \sqrt{kn_1}(\mu - \mu_0)/\sigma = \sqrt{k}\vartheta_1$.
- $\text{Cor}(Z_j^*, Z_k^*) = \sqrt{\min(j,k)/\max(j,k)}$ for all $1 \leq j, k \leq K$
- $(Z_1^*, \ldots, Z_K^*)$ is multivariate normal distributed.

Classical Designs

without
futility stopping

The designs of Pocock and O'Brien & Fleming

Rejection regions with rejection bounds u_k, $k = 1, \ldots, K$:

$$\mathcal{R}_k^* = \left\{ |Z_k^*| \geq u_k \right\} = (-\infty, -u_k) \cup (u_k, \infty),$$

$\mathcal{A}_k^* = \emptyset$, $\mathcal{C}_k^* = (-u_k, u_k)$ for $k < K$, and $\mathcal{A}_K^* = (-u_K, u_K)$.

- **Design of Pocock (1977):** Constant rejection bounds, i.e.

$$u_1 = \cdots = u_K = c_{\mathrm{P}}$$

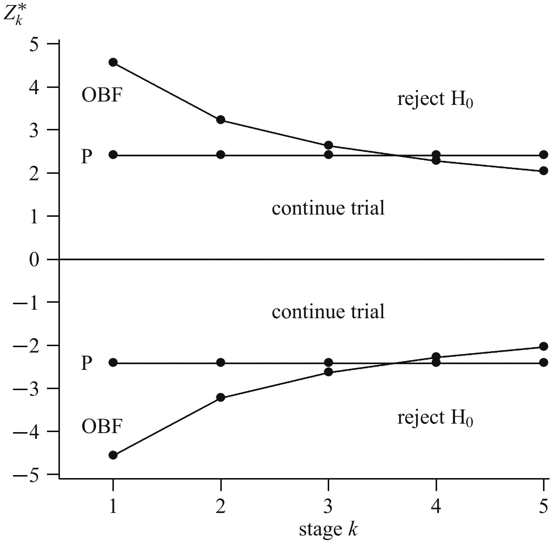
with $c_{\mathrm{P}} = c_{\mathrm{P}}(K, \alpha)$ such that $\mathbf{P}_{\mu_0}\left(\bigcup_{k=1}^{K} \left\{ |Z_k^*| \geq c_{\mathrm{P}} \right\} \right) = \alpha$

- **Design of O'Brien & Fleming (1979):** Decreasing rejection bounds with

$$u_k = c_{\mathrm{OBF}} / \sqrt{k}$$

with $c_{\mathrm{OBF}} = c_{\mathrm{OBF}}(K, \alpha)$ s.th. $\mathbf{P}_{\mu_0}\left(\bigcup_{k=1}^{K} \left\{ |Z_k^*| \geq c_{\mathrm{OBF}} / \sqrt{k} \right\} \right) = \alpha$

Examples for Pocock and O’Brien & Fleming Designs



Two-Sided O’Brien and Fleming’s (OBF)

and

Pocock’s (P) design

for $H_0 : \mu = 0$

for equal stage sizes

with $K = 5$ stages

and $\alpha = 0.05$

This is Figure 2.1 in WaBr16;

see also Tables 2.1 and 2.2 in WaBr16.

Comment on the O'Brien & Fleming design

We assume here for simplicity that $\mu_0 = 0$ and $\sigma = 1$.

Since $Z_k^* = \sum_{l=1}^{k} Z_l / \sqrt{k}$ with the stage-wise z-scores, and

$$Z_l = \sum_{j=1}^{n} X_{lj} \Big/ \sqrt{n},$$

we obtain that $|Z_k^*| \geq c_{\mathrm{OBF}} / \sqrt{k}$ is equivalent to

$$\sqrt{nk}|Z^*| = |\sum_{l=1}^{k} \sum_{j=1}^{n} X_{lj} \geq \sqrt{n}\, c_{\mathrm{OBF}}.$$

Hence, we use a constant boundary for the sum of observations;

is in line with the *Sequential Likelihood Ratio Test* of Wald & Barnard.

Formulation via *local levels*

One can formulate a GSD in terms of the local p-values

$$p_k^* := 2\Big(1 - \Phi\big(|Z_k^*|\big)\Big), \quad k = 1, \dots, K$$

Namely: $\quad |Z_k^*| \geq u_k \quad \Longleftrightarrow \quad p_k^* \leq \alpha_k := 2\big(1 - \Phi(u_k)\big)$

- Constant *local levels* in the Pocock design:

$$\alpha_1 = \cdots = \alpha_K = 2\Big(1 - \Phi\big(c_{\mathrm{P}}\big)\Big)$$

- Decreasing *local levels* of the O'Brien & Fleming design:

$$\alpha_k = 2\Big(1 - \Phi\big(c_{\mathrm{OBF}}/\sqrt{k}\big)\Big), \quad k = 1, \dots, K$$

- Table 2.2 in WaBr16 (p.29) gives u_k and α_k of the Pocock and O'Brien & Fleming designs for $\alpha = 0.05$ up to 5 stages.

Discussion of the two designs

- The more stages K, the larger the rejection boundaries, i.e. more adjustment is required with more stages.
- With the O'Brien& Fleming design the early rejection bounds are large and early rejections are rather unlikely, at least under H_0.
- With the Pocock design early rejections are more likely.
- With the O'Brien& Fleming design the last rejection bound is close to the un-adjusted bound $z_{\alpha/2}$. This is not the case for Pocock's design.
- In practice, the O'Brien & Fleming design is generally preferred, since early rejection without overwhelming evidence may not be convincing (e.g. because of too little safety data).

Power and Sample size

- As argued before, the maximum sample size N_K required for power $1-\beta$ is a multiple of the fixed size

$$n_f = (z_{\alpha/2} + z_\beta)^2/\delta_1^2,$$

i.e.

$$N_K = n_f \cdot I(K, \alpha, \beta)$$

- The *inflation factor* $I(K, \alpha, \beta)$ depends on the type of design, e.g. whether Pocock or O'Brien & Fleming.
- Table 2.3 in WaBr16 gives $I = I(K, \alpha, \beta)$ of the Pocock and O'Brien & Fleming design for several K and typical α and β.
- One sees from this table that Pocock's design leads to larger maximum sample sizes N_K than the O'Brien & Fleming design.

Numerical Examples

We choose $\alpha = 0.05$, $\beta = 0.2$ and $\delta_1 = 0.5$

$$\longrightarrow \quad n_f = (z_{0.025} + z_{0.2})^2/0.25 = 31.4$$

- **O'Brien & Fleming with $K = 4$:**
  We read $I = 1.024$ from Table 2.3 in WaBr16, which implies

  $$N_K = 1.024 \cdot 31.4 = 32.2 \quad \rightarrow \quad n = N_K/4 = 8.05$$

  Hence, for power 80% we need $n = 9$ patients per stage.

- **Pocock with $K = 4$:**
  We read $I = 1.202$ from Table 2.3 in WaBr16, which implies

  $$N_K = 1.202 \cdot 31.4 = 37.7 \quad \rightarrow \quad n = N_K/4 = 9.4$$

  Hence, for power 80% we need $n = 10$ patients per stage.

Average Sample Size

- The required stage-wise sample size is

$$n = N_K/K = n_f \cdot I(K, \alpha, \beta)/K$$

- Consequently, we get for the ASN (see p.16 in WaBr16 or Slide 29 for Chapter 1) relative to n_f:

$$\frac{\text{ASN}(\mu)}{n_f} = \frac{I(K, \alpha, \beta)}{K} \underbrace{\left(1 + \sum_{k=2}^{K} \mathbf{P}_{\vartheta_1}\left(Z_1^* \in \mathcal{C}_1^*, \ldots, Z_{k-1}^* \in \mathcal{C}_{k-1}^*\right)\right)}_{\text{average number of stages}}$$

- Since β determines the ncp $\vartheta_{1,\beta}$ uniquely, the fraction ASN/n_f is uniquely determined by design and power (and beyond that is independent from δ_1).
- Table 2.3 in WaBr16 also gives ASN/n_f (numbers in bracket).

Back to the numerical Examples (Slide I)

As before: $K = 4$, $\alpha = 0.05$, $\beta = 0.2$ and $n_f = 31.4$.

- **O'Brien & Fleming:**
  We read ASN$/n_f = 0.831$ from Table 2.3, which implies

$$ASN = 0.831 \cdot 31.4 = 26.1$$

- **Pocock:**
  We read ASN$/n_f = 0.805$ from Table 2.3, which implies

$$ASN = 0.805 \cdot 31.4 = 25.3$$

- **Summary:** Pocock has larger maximum but smaller expected sample sizes at the planning alternative.

Back to the numerical Examples (Slide II)

- With Pocock's design we have a higher chance to stop early:

Stopping probabilities (at planning alternative):

Stage	1	2	3
OBF	0.4%	19.1.%	35.7%
Pocock	20.5%	25.2%	34.0%

- The higher the chance to stop early, the smaller the expected sample size.
- However, this comes for the price of a larger maximum sample size with the Pocock design.

Back to the numerical Examples (Slide III)

- Figure 2.2 in WaBr16 shows the expected sample size in dependence of $\delta = (\mu - \mu_0)/\sigma$.
- One can see that Pocock gives a smaller ASN only for larger δ.
- For smaller δ the ASN is close to the maximum sample size $N_K = Kn$, which is smaller for OBF.
- *Final remark:* Since n is smaller for OBF and ASN(δ) $\approx n$ for large δ, the ASN becomes smaller again for OBF when δ or K becomes very large; see Figure 2.3 in WaBr16.
- **Exercise:** Investigate this with the `gsDesign` package in `R`.

Important remarks on the number of stages

- One can see from Table 2.3 that the expected sample size decreases with the number of stages K, while the maximum sample size increases.
- There is a relevant decrease in the ASN already with $K = 2$ stages.
- With increasing K the gain in ASN becomes smaller and smaller.
- With the designs of OBF and Pocock the gain in the ASN becomes relatively small for $K \geq 5$.
- Interim analyses produce costs and bear the danger of bias. Hence, in practice usually only $K \leq 5$ stages are used.

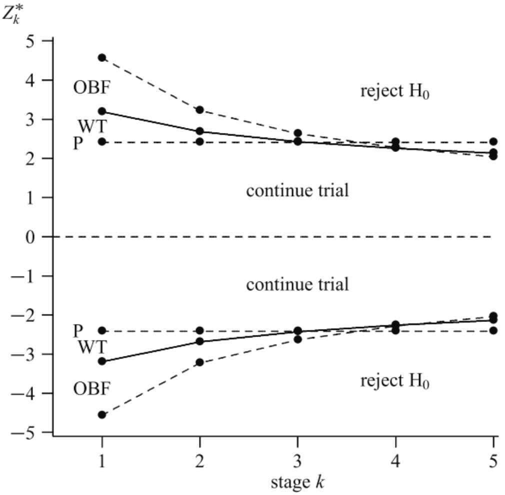
Power family of Wang & Tsiatis

- Wang & Tsiatis (1987) suggest the rejection boundaries

$$u_k = c_{\mathrm{WT}}(K, \alpha, \beta, \Delta) k^{\Delta - 0.5}$$

- The family of bounds is also called Δ-class.
- For $\Delta = 0$ we obtain the O'Brien & Fleming boundaries.
- For $\Delta = 0.5$ we obtain Pocock's boundaries.
- For $0 < \Delta < 0.5$ we obtain a compromise between P and OBF.

Wang & Tsiatis boundaries



Wang & Tsiatis Δ-class:

$$u_k = c_{\mathrm{WT}}\, k^{\Delta - 0.5}$$

Choice of c_{WT} is such that type I error is α.

– *Special cases:*

O'Brien & Fleming: $\Delta = 0$

Pocock: $\Delta = 0.5$

See Table 2.4 in WaBr16 for more examples.

Maximum and expected sample size for the Δ-class

- Table 2.5 in WaBr16 gives the maximum sample size and ASN (at the planning alternative), both relative to n_f.
- The bounds for $\Delta = 0.4$ beat the Pocock bounds with regard to maximum and average sample size.
- Wang & Tsiatis (1987) determine the Δ for which the ASN is minimal under the planing alternative (Table 2.6 in WaBre16)

Examples for $\alpha = 0.05$:

	$1-\beta=0.5$			$1-\beta=0.8$			$1-\beta=0.9$		
K	Δ	I	$\frac{ASN}{n_f}$	Δ	I	$\frac{ASN}{n_f}$	Δ	I	$\frac{ASN}{n_f}$
2	0.18	1.03	0.96	0.42	1.08	0.85	0.49	1.10	0.78
5	0.08	1.04	0.93	0.35	1.11	0.78	0.44	1.16	0.68

- Wang & Tsiatis (1987) found that the optimal Δ-boundaries are similar to general optimum determined by Pocock (1982).

Classical Designs

with binding futility stopping

Symmetric designs (Slide I)

- Pampallona & Tsiatis (1994) suggest to use a GSD with a symmetric interim acceptance region:

$$\mathcal{A}_k^* = [-u_k^0, u_k^0], \quad \mathcal{C}_k^* = (-u_k^1, -u_k^0) \cup (u_k^0, u_k^1), \quad k = 1, \ldots, K$$

for specific $0 < u_k^0 < u_k^1$ $(k < K)$ and $0 < u_K^0 = u_K^1$.

- Rejection regions: $\mathcal{R}_k^* = (-\infty, -u_k^1) \cup (u_k^1, \infty)$, $1 \leq k \leq K$.
- This means to accept H_0 at stage k if $|Z_k^*| \leq u_k^0$,

  and to reject H_0 a stage k if $|Z_k^*| \geq u_k^1$

- Choice of rejection boundaries:

$$u_k^1 = c^1(K, \alpha, \beta, \Delta) k^{\Delta - 0.5} \qquad (2.1)$$

Symmetric designs (Slide II)

- Choice of the acceptance ("futility") boundaries:

$$u_k^0 = \vartheta_k - c^0(K, \alpha, \beta, \Delta) k^{\Delta - 0.5} \qquad (2.2)$$

where $\vartheta_k = \mathbf{E}_{\mu_1}(Z_k^*) = \sqrt{kn}\,\delta_1$ is the planning ncp.

- **Rational:** Think of testing $\tilde{H}_1 : |\delta| \geq \delta_1$ (as null) at level β.

Since $Z_k^* \mp \vartheta_k \sim_{\delta = \pm\delta_1} N(0, 1)$, rejection of $\tilde{H}_1$ is best done by

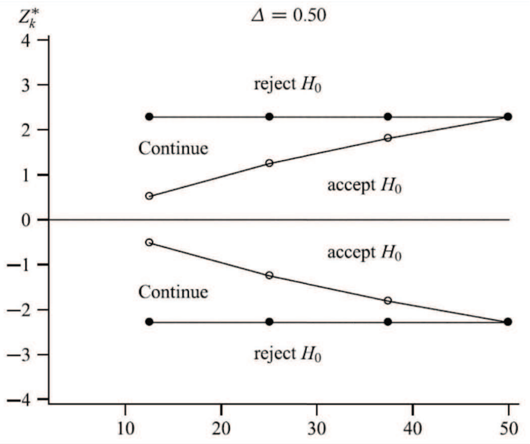
$$Z_k^* - \vartheta_k \leq -d_k^0 \quad \Longleftrightarrow \quad Z_k^* \leq \vartheta_k - d_k^0$$

and

$$Z_k^* + \vartheta_k \geq d_k^0 \quad \Longleftrightarrow \quad Z_k^* \geq -(\vartheta_k - d_k^0)$$

The two rejection rules can be summarized as: $|Z_k^*| \leq \vartheta_k - d_k^0$

Example for Pampallona and Tsiatis boundaries



Pampallona & Tsiatis design:

– *Rejection boundaries*

$$u_k^1 = c^1$$

– *Acceptance boundaries:*

$$u_k^0 = \vartheta_k - c^0$$

– Choice of c^1 and c^0 is such that type I & II errors are α & β.

Here: $\Delta = 0.5$, $K = 4$, $\alpha = 0.05$ and $1 - \beta = 0.8$.

Determination of c^0 and c^1 (Slide 1)

- Want to choose $c^0 = c^0(K, \alpha, \beta, \Delta)$ and $c^1 = c^1(K, \alpha, \beta, \Delta)$ such that pre-specified type I and II errors, α and β, are **both** met.
- Simultaneous control of α and β via the decision boundaries is main reason for the name "symmetric designs".
  (Before, we focused solely on α in the determination of boundaries.)
- **Problem:** u_k^0 seem to depend on δ_1 (i.e. μ_1) and n via ϑ_k!
- By the definition of u_k^0, u_k^1 and the identity $u_K^0 = u_K^1$ we obtain:

$$\vartheta_K = \sqrt{Kn}\,\delta_1 = (c^0 + c^1)K^{\Delta-0.5}$$

which implies

$$\vartheta_k = \sqrt{kn}\delta_1 = \sqrt{k}(c^0 + c^1)K^{\Delta-1}, \quad k = 1, \ldots, K. \qquad (2.3)$$

Determination of c^0 and c^1 (Slide 2)

- By formula (2.3) we can remove the dependency on δ_1 and n:

$$u_k^1 = c^1 k^{\Delta - 0.5} \quad \text{and} \quad u_k^0 = \left[\sqrt{k/K}(c^0 + c^1) - c^0\right] K^{\Delta - 0.5}$$

- By two-dimensional root finding one can determine c^0 and c^1 such that

$$\mathbf{P}_{\vartheta_1 = 0}\Big(\text{reject } H_0\Big) = \alpha \quad \text{and} \quad \mathbf{P}_{\vartheta_1 = \vartheta_1^*}\Big(\text{reject } H_0\Big) = 1 - \beta$$

where $\quad \vartheta_1^* := (c^0 + c^2) K^{\Delta - 1}$.

- These bounds do only depend on α, β, K and Δ, i.e.

$$c^0 = c^0(K, \alpha, \beta, \Delta) \quad \text{and} \quad c^1 = c^1(K, \alpha, \beta, \Delta)$$

Sample size calculation

- Described choice of c^0 and c^1 guarantees type I rate α.
- It guarantees type II error $\leq \beta$, if the first stage Z_1^* has expectation

$$\vartheta_1 = \sqrt{n}(\mu - \mu_1)/\sigma \geq \vartheta_1^* = (c^0 + c^2)K^{\Delta - 1}$$

- Given the planning alternative μ_1, this leads to the formula

$$n \geq \left(\frac{(c^0 + c^1)K^{\Delta-1}}{\delta_1} \right)^2, \qquad \delta_1 := (\mu_1 - \mu_0)/\sigma$$

  for the *stage-wise sample size*, and for the *maximum sample size:*

$$N_K = Kn \geq \left[(c^0 + c^1)K^{\Delta - 0.5}/\delta_1 \right]^2$$

- Note the similarity to the formula for the single-stage z-test!

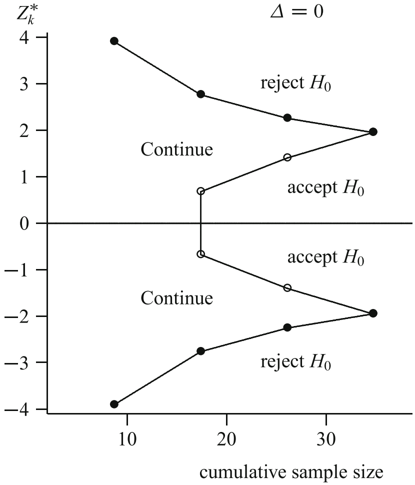
Important remark / extension

- We cannot always satisfy both, the type I and type II error condition, by the choice for (2.1) and (2.2) of the rejection and acceptance boundaries.
- Both conditions can be fulfilled, if we permit starting acceptance of H_0 at some later stage $k^* > 1$.
- This means to set $u_k^0 := 0$ for all $k < k^*$.
- The method can be implemented by using the acceptance bounds

$$u_k^0 := \max\left(\underbrace{\left[\sqrt{k/K}(c^0 + c^1) - c^0\right] K^{\Delta - 0.5}}_{\text{the original } u_k^0}, 0\right)$$

where k^* is simply the smallest k with $\sqrt{k/K} > c^0/(c^0 + c^1)$.

Example boundaries



Pampallona & Tsiatis design:

– *Rejection boundaries*

$$u_k^1 = c^1\, k^{-0.5}$$

– *Acceptance boundaries:*

$$u_k^0 = \max\left(\vartheta_k - c^0\, k^{-0.5}, 0\right)$$

with $\vartheta_k = \sqrt{k}(c^0 + c^1)K^{-1}$

– Choice of c^1 and c^0 is such that type I & II errors are α & β.

Here: $\Delta = 0$, $K = 4$, $\alpha = 0.05$ and $1 - \beta = 0.8$.

The example numerically

- $K = 4$, $\Delta = 0$, $\alpha = 0.05$, $\beta = 0.2$
- Table 2.7 in WaBr16: $c^0 = 1.9892$ and $c^1 = 3.9055$
- $\vartheta_k = \sqrt{k}(c^0 + c^1)/K = \sqrt{k} \cdot 1.4738$
- $$u_1^0 = 1.4738 - 1.9892 < 0 \quad \rightarrow \quad u_1^0 = 0$$
  $$u_2^0 = \sqrt{2} \cdot 1.4738 - 1.9892 = 0.678$$
  $$u_3^0 = \sqrt{3} \cdot 1.4738 - 1.9892 = 1.404$$
  $$u_4^0 = \sqrt{4} \cdot 1.4738 - 1.9892 = 1.953$$
- $$u_1^1 = 3.9055, \quad u_1^2 = 3.9055/\sqrt{2} = 2.762$$
  $$u_1^2 = 3.9055/\sqrt{3} = 2.255, \quad u_1^2 = 3.9055/\sqrt{4} = 1.953$$

Sample sizes in the example

- We plan for the relative effect $\delta_1 = 0.5$
- Sample size for fixed sample z-test:

$$n_f = (1.96 + 0.842)^2 / 0.5^2 = 31.4$$

- Table 2.7 in WaBr16: inflation factor for design is $I = 1.107$
- Hence, $\quad N_K \geq 1.107 \cdot 31.4 = 34.8 \quad$ and $\quad n \geq 34.8/4 = 8.7$

$$\rightarrow \; n = 9 \quad \rightarrow \; N_K = 4 \cdot 9 = 36$$

- Expected sample sizes (see Table 2.7. in WaBr16):

  $\text{ASN}(0) = 0.722 \cdot 36 = 26.0$

  $\text{ASN}(\delta_1) = 0.802 \cdot 36 = 28.9$

One-Sided Designs

Introduction

- We consider now the one-sided hypotheses

$$H_0 : \mu \leq \mu_0 \qquad \text{against} \qquad H_1 : \mu > \mu_0$$

- Without early acceptance we would now choose

$$\mathcal{C}_k^* = (-\infty, u_k), \quad \mathcal{A}_k^* = \emptyset, \quad k = 1, \dots, K-1$$

$$\mathcal{R}_k^* = [u_k, \infty), \quad k = 1, \dots, K, \quad \mathcal{A}_K^* = (-\infty, u_K).$$

- Type I error rate control:

$$\mathbf{P}_{\mu_0}\left(\bigcup_{k=1}^{K}\left\{Z_k^* \geq u_k\right\}\right) = \alpha$$

Δ-class of Wang & Tsiatis (1987)

- We choose

$$u_k = c_{WT}(K, \alpha, \Delta) k^{\Delta - 0.5}$$

- $\Delta = 0.5 \quad \rightarrow \quad$ one-sided Pocock design
- $\Delta = 0 \quad \rightarrow \quad$ one-sided O'Brien & Fleming design

- In the one-sided case, sample sizes are "based" on the one-sided fixed size sample z-test

$$n_f = \left(z_{\alpha} + z_{\beta}\right) / \delta_1^2$$

Two-sided versus one-sided boundaries

- As for single stage tests, the *two-sided boundaries at level* α appear to be identical to the *one-sided boundaries at level* $\alpha/2$;

  compare Tables 2.1 and 2.9 (last column) in WaBr16.
- This is only a numerical coincidence and approximately true.
- We illustrate this for the case $K = 2$: The type I error of the two-sided GSD is

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

$$2\Big\{\underbrace{\mathbf{P}\big(Z_1^* \geq u_1\big) + \mathbf{P}\big(Z_1^* < u_1,\ Z_2^* \geq u_2\big)}_{\text{level of one-sided test}} - \underbrace{\mathbf{P}\big(Z_1^* < -u_1,\ Z_2^* \geq u_2\big)}_{\approx 0}\Big\}$$

Numerical comparison and conclusion

- P_1 is the type I error rate of the one-sided and P_2 of the two-sided test with $u = u_1 = u_2$:

u	0.4	0.8	1.2	1.6	2.0	2.4
P_1	0.87	0.598	0.3470	0.174531	0.0759732	0.0285025575
P_2	0.92	0.602	0.3472	0.174533	0.0759732	0.0285025575

- For sufficiently large u_k, we can use boundaries of the two-sided GSD at level α (e.g. 0.05) for the one-sided GSD at level $\alpha/2$ (0.025).

- However, to be on the safe side, it is recommended to do the calculations for the one-sided GSD.

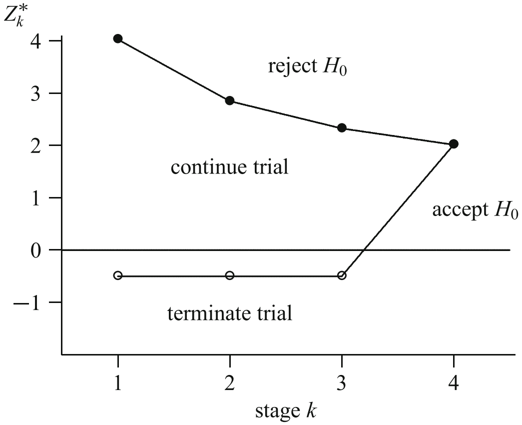
One-sided GSD with early acceptance

- DeMets & Ware (1980, 1982) suggest to use a constant futility boundary $u^L < u_k$ for all $k \leq K - 1$.
- With this futility boundary the decision regions become

$$\mathcal{C}_k^* = (u^L, u_k), \quad \mathcal{A}_k^* = (-\infty, u^L), \quad k = 1, \ldots, K-1$$

$$\mathcal{R}_k^* = (u_k, \infty), \quad k = 1, \ldots, K, \quad \mathcal{A}_K^* = (-\infty, u_K)$$

One-sided boundaries



DeMets & Ware design:

– fix early acceptance (futility) bound

$$u^L \in [-\infty, \infty)$$

– one-sided rejection bounds

$$u_k^1 = c_{DW}\, k^{\Delta - 0.5} > u_L$$

– Choose c_{DW} such that type I error is α.

(Figure 2.6 of WaBr16)

No futility stop iff $u^L = -\infty$.

Properties of One-sided GSD with early acceptance

- See Table 2.9 in WaBr16.
- Notice that rejection boundaries u_k increase with decreasing u^L
- Rejection boundaries u_k change only little with u^L for small K.
- Non-constant $u^L = u_k^L$ where also suggested by DeMets & Ware and others.

Symmetrical designs of Pampalona & Tsiatis (1994)

- We use one-sided acceptance u_k^0 and rejection boundaries u_k^1:

$$u_k^0 = \vartheta_k - c^0(K, \alpha, \beta, \Delta) k^{\Delta - 0.5}, \quad k = 1, \dots, K$$

$$u_k^1 = c^1(K, \alpha, \beta, \Delta) k^{\Delta - 0.5}, \quad k = 1, \dots, K$$

$$u_K^0 = u_K^1 \quad \longrightarrow \quad \vartheta_k = \sqrt{k}(c^0 + c^1) K^{\Delta - 1}, \quad k = 1, \dots, K$$

- We choose u_k^0 and u_k^1 such that

$$\mathbf{P}_0\left(Z_1^* \geq u_k^1\right) + \sum_{k=2}^{K} \mathbf{P}_0\left(u_j^0 < Z_j^* \leq u_j^1, \, j < k, \; Z_k^* \geq u_k^1\right) = \alpha$$

$$\mathbf{P}_{\vartheta_1}\left(Z_1^* \geq u_k^1\right) + \sum_{k=2}^{K} \mathbf{P}_{\vartheta_1}\left(u_j^0 < Z_j^* \leq u_j^1, \, j < k, \; Z_k^* \geq u_k^1\right) = 1 - \beta$$

Comments on symmetrical one-sided designs

- Like for two-sided GSD this method controls the type I and II errors rates per design.
- See Tables 2.11 and 2.12 as well as Figure 2.7 in WaBr16 for examples.
- The Tables also contain the inflation factor I as well as average sample sizes under

$$\vartheta_1 = \quad 0, \quad \frac{c^0 + c^1}{2} K^{\Delta - 1}, \quad (c^0 + c^1) K^{\Delta - 1}.$$

- The Pampalona & Tsiatis designs behaves favourable with respect to the average sample sizes.
- Given $\vartheta_1 = (c^0 + c^1) K^{\Delta - 1}$ and the planning effect size δ_1 the stage wise sample size need to be chosen such that

$$n \geq (\vartheta_1 / \delta_1)^2$$

Binding vs. non-binding futility boundaries

- In the trial, one may **not** wish to stop when $Z_k^* \leq u^L$, e.g. because of promising results in secondary endpoints.
- However, ignoring the futility boundary will lead to an inflation of the type I error rate.
- **Solution:** Calculate rejection bound u_k^1 under the assumption of no futility stopping ($u^L = -\infty$) even though we choose $u^L > -\infty$.
- Stopping for futility then leads to a type I error rate $< \alpha$.
- The finite u^L should be accounted for in the power and sample size calculation. The power is then by sure $\geq 1 - \beta$.
- *Advantage:*

  We have the option to stop with acceptance of H_0 if $Z_k^* \leq u^L$, and we having type I and II error rates by sure under control.

Two-sided as two one-sided GSD (Slide I)

- Two-sided GSD are commonly used even though the one-sided null hypothesis
$$H^{(+)} : \mu \leq \mu_0$$
is of most relevance for clinical trials.
- Classical two-sided z- and t-tests can be understood as two one-sided tests at level $\alpha/2$.
- This is also true for group sequential designs, however in a more complex sense.
- A two-sided GSD **without** early acceptance is like two one-sided GSD **with** binding early acceptance:

  If at some stage k, $Z_k^* < -u_k$, then $H^{(+)}$ must be accepted (and the trial is stopped).

Two-sided as two one-sided GSD (Slide II)

- In general, we have for the decision regions of a two-sided GSD:

$$\mathcal{C}_k^* = \mathcal{C}_k^{*(-)} \cup \mathcal{C}_k^{*(+)}, \quad \mathcal{R}_k^* = \mathcal{R}_k^{*(-)} \cup \mathcal{R}_k^{*(+)} \quad \mathcal{A}_k^* = \mathcal{A}_k^{*(-)} \cup \mathcal{A}_k^{*(+)}$$

  with negative and positive parts indexed by $(-)$ and $(+)$.
- We reject $H_0^{(+)} : \mu \leq \mu_0$ at stage k if $Z_k^* \in \mathcal{R}_k^{*(+)} = [u_k^1, \infty)$,
- and use for $H_0^{(+)}$ the continuation rejection $\mathcal{C}_k^{*(+)} = (u_k^0, u_k^1)$.
- This means to accept $H_0^{(+)}$ also if $Z_j^* \in \mathcal{C}_j^{*(-)}$ at some stage j.
- The probability that $Z_j^* \in \mathcal{C}_j^{*(-)}$ and $Z_k^* \geq u_k^1$ for some $k > j$ is usually small (in particular under the alternative).

  In this case the stage wise z-scores have “conflicting directions”.
- If early acceptance is binding, the resulting one-sided GSD is somewhat conservative (has level > $\alpha/2$).