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# Testing a Primary and a Secondary Endpoint in a Confirmatory Group Sequential Clinical Trial

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# Motivating Example

- **CAPTURE:** clinical trial of placebo vs. abciximab for coronary intervention in refractory unstable angina (1997)
- Primary endpoint was a composite of **death, MI or urgent intervention for recurrent ischemia** within 30 days
- Secondary endpoint was **death or MI** within 30 days
- Expect 15% event rate for placebo on primary endpoint
- Enroll 1400 patients; 80% power for a 1-sided level 0.025 test to detect a 5% drop in event rate with abciximab
- One interim analysis planned for possible early stopping
- Test primary and secondary endpoints hierarchically

# Two-Stage Design: Notation

- Let  $(n_1, n_2)$  be the cumulative sample sizes at (Stage 1, Stage 2)
- **Primary Statistics:**  $(X_1, X_2)$  at (Stage 1, Stage 2) are distributed thus:

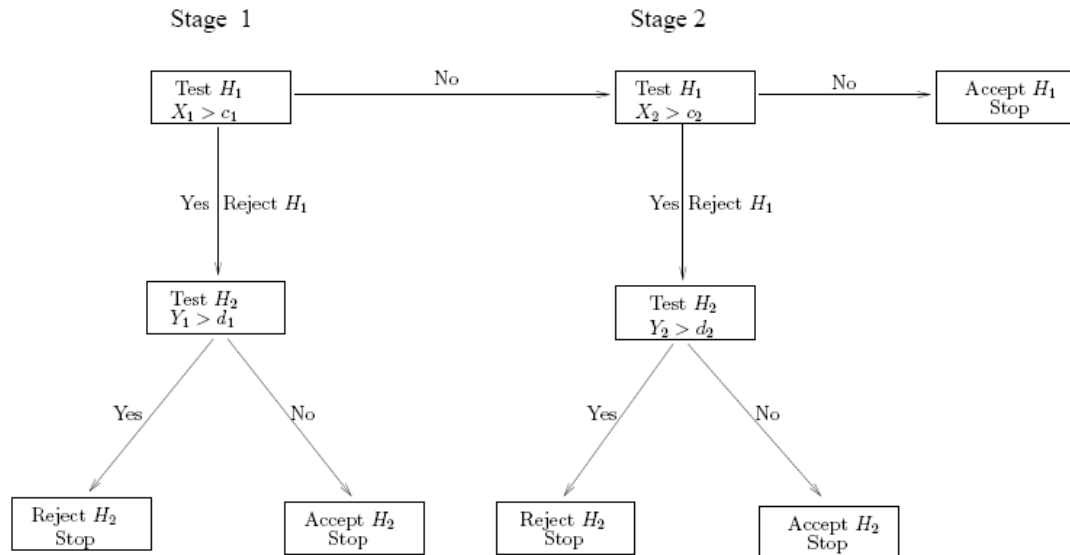
$$X_1 \sim N(\delta_1 \sqrt{n_1}, 1); \quad X_2 \sim N(\delta_1 \sqrt{n_1 + n_2}, 1)$$

- **Secondary Statistics:**  $(Y_1, Y_2)$  at (Stage 1, Stage 2) are distributed thus:

$$Y_1 \sim N(\delta_2 \sqrt{n_1}, 1); \quad Y_2 \sim N(\delta_2 \sqrt{n_1 + n_2}, 1)$$

- $\text{corr}(X_1, X_2) = \text{corr}(Y_1, Y_2) = \sqrt{\frac{n_1}{n_1 + n_2}}$
- $\text{corr}(X_1, Y_1) = \text{corr}(X_2, Y_2) = \rho$
- Interested in testing  $H_j: \delta_j = 0$ , for  $j = 1, 2$  and controlling FWER

# Hierarchical Group Sequential Testing Procedure



## Control of FWER

- Suppose interim analysis planned after 50% of the data arrive
- O'Brien-Fleming 1-sided level-0.025 boundaries are adopted for the primary efficacy endpoint:

$$c_1 = 1.98\sqrt{2}, \quad c_2 = 1.98$$

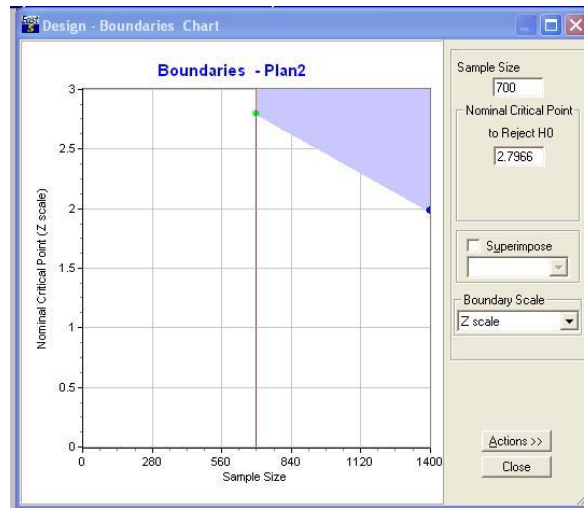
- With these boundaries it can be shown that

$$P_{H_1}(X_1 \geq c_1) + P_{H_1}(X_1 < c_1, X_2 \geq c_2) = 0.025$$

FWER is controlled under  $H_1 \cap H_2$  or  $H_1 \cap \overline{H_2}$

- **Question:** How to select  $(d_1, d_2)$  for the secondary efficacy endpoint such that  $\text{FWER} \leq 0.025$  under  $\overline{H_1} \cap H_2$ ?

# OF Boundaries at Level-0.025 for Primary Endpoint



If  $H_1$  is true, FWER = 0.025 regardless of truth or falsity of  $H_2$

## Protecting FWER under $\overline{H_1} \cap H_2$

- Hereafter, assume that all probabilities are computed under  $\delta_1 > 0$  and  $\delta_2 = 0$

- Define  $\Delta_1 = \delta_1 \sqrt{n_1}$ ,  $\Delta_2 = \delta_1 \sqrt{n_1 + n_2}$

- Thus, for  $j = 1, 2$ ,

$$X_j \sim N(\Delta_j, 1), \quad Y_j \sim N(0, 1), \quad \text{corr}(X_j, Y_j) = \rho$$

- The FWER is given by

$$\text{FWER} = P(X_1 \geq c_1, Y_1 \geq d_1) + P(X_1 < c_1, X_2 \geq c_2, Y_2 \geq d_2)$$

- Given  $(c_1, c_2)$  is level- $\alpha$ , find  $(d_1, d_2)$  such that  $\text{FWER} \leq 0.025$

# General Expression for FWER

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$$\text{FWER} = \int_{c_1 - \Delta_1}^{\infty} \Phi\left(\frac{-d_1 + \rho u}{\sqrt{1 - \rho^2}}\right) \phi(u) du \\ + \int_{c_2 - \Delta_2}^{\infty} \Phi\left(\frac{c_1 - \Delta_1 - \gamma u}{\sqrt{1 - \gamma^2}}\right) \Phi\left(\frac{-d_2 + \rho u}{\sqrt{1 - \rho^2}}\right) \phi(u) du$$

where  $\Delta_1 = \delta_1 \sqrt{n_1}$ ,  $\Delta_2 = \delta_1 \sqrt{n_1 + n_2}$ , and  $\gamma = \sqrt{\frac{n_1}{n_1 + n_2}}$

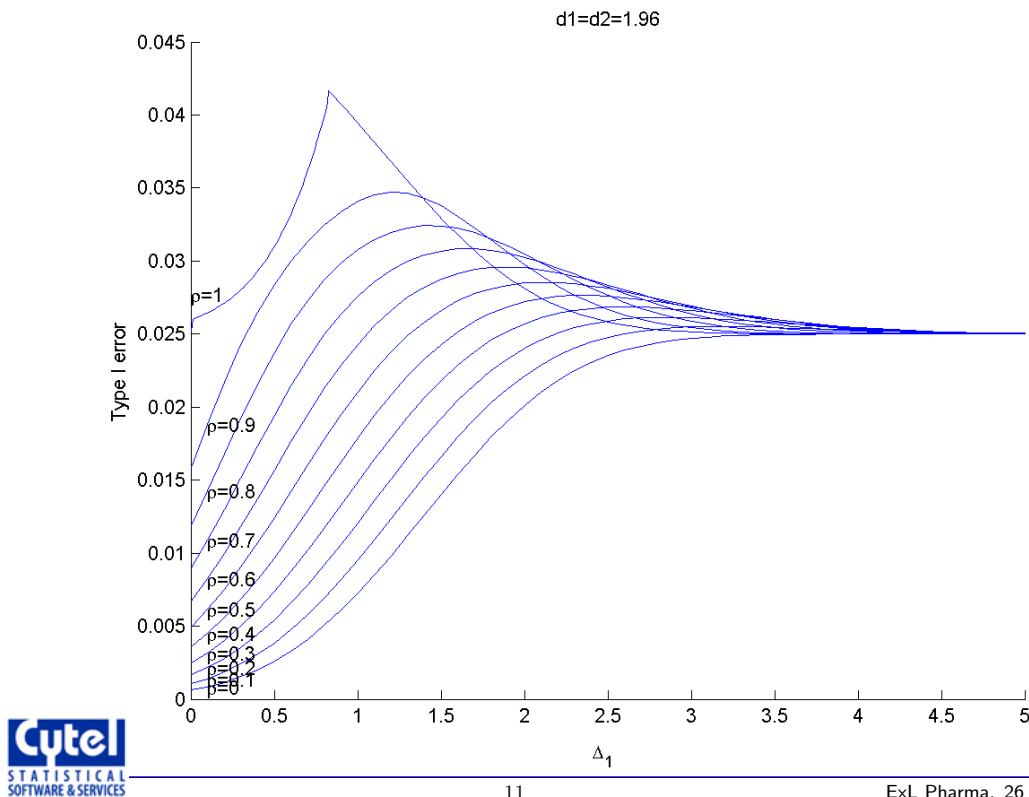
- FWER depends on  $\delta_1$  and  $\rho$ , both of which are unknown
- Find  $(d_1, d_2)$  such that  $\text{FWER} \leq \alpha$  regardless of  $\delta_1$  and  $\rho$

## 1. $d_1 = d_2 = z_\alpha$ won't work

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- In single-stage designs we may test  $H_2$  at level  $\alpha$  provided a level- $\alpha$  test of  $H_1$  acts as a gatekeeper
- It is natural to try the same strategy for two-stage designs; i.e., test  $H_2$  at level  $\alpha$  the first time that  $H_1$  rejects
- This strategy fails. We have proven that:
  - $\text{FWER} \leq \alpha$  if  $\rho = 0$
  - $\max_{\Delta_1} \text{FWER} > \alpha$  if  $\rho = 1$
  - $\text{FWER} \rightarrow \alpha$  as  $\Delta_1 \rightarrow \infty$  for all  $\rho \geq 0$

## FWER with $(c_1 = 1.98\sqrt{2}, c_2 = 1.98)$ , and $(d_1 = d_2 = 1.96)$



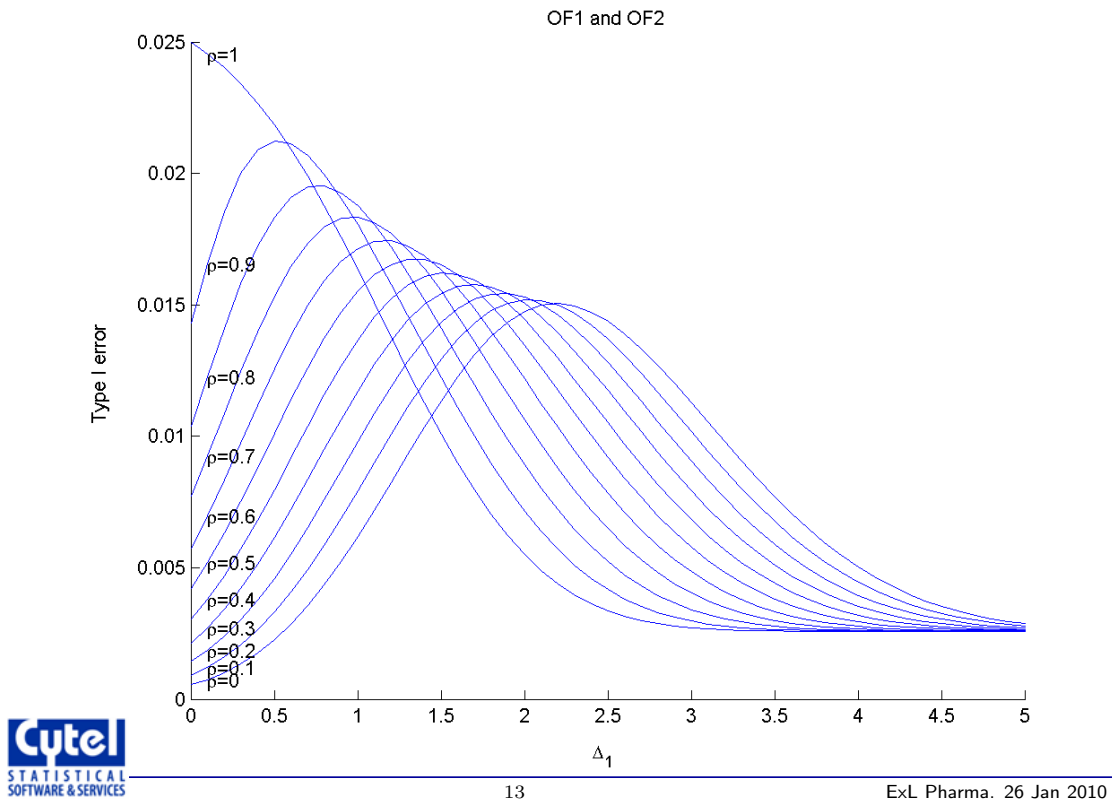
## 2. $\text{FWER} \leq \alpha$ if $(d_1, d_2)$ is level- $\alpha$

We consider three cases:

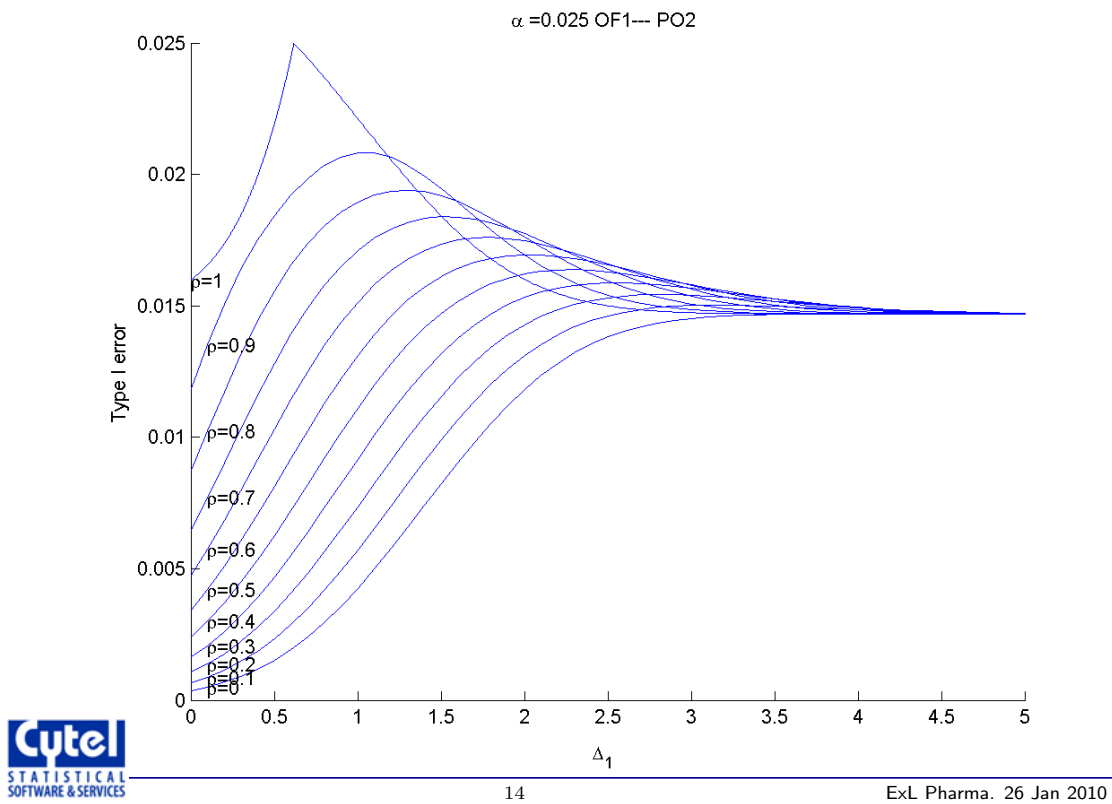
1. If  $c_1 = d_1, c_2 = d_2$ , then for  $\rho = 1$ ,  $\max_{\Delta_1} \text{FWER} = \alpha$  and is attained at  $\Delta_1 = 0$
2. If  $c_1 > d_1, c_2 < d_2$  (OF primary, PO secondary), then for  $\rho = 1$ ,  $\max_{\Delta_1} \text{FWER} = \alpha$  and is attained at  $\Delta_1 = c_1 - d_1$
3. If  $c_1 < d_1, c_2 > d_2$  (PO primary, OF secondary), then for  $\rho = 1$ ,  $\max_{\Delta_1} \text{FWER} < \alpha$  and is attained at 
$$\Delta_1 = (c_1 - d_1) \sqrt{\frac{n_1}{n_1 + n_2}}$$

Assume  $c_1 = 1.98\sqrt{2}, c_2 = 1.98$  (OF boundry at level 0.025)

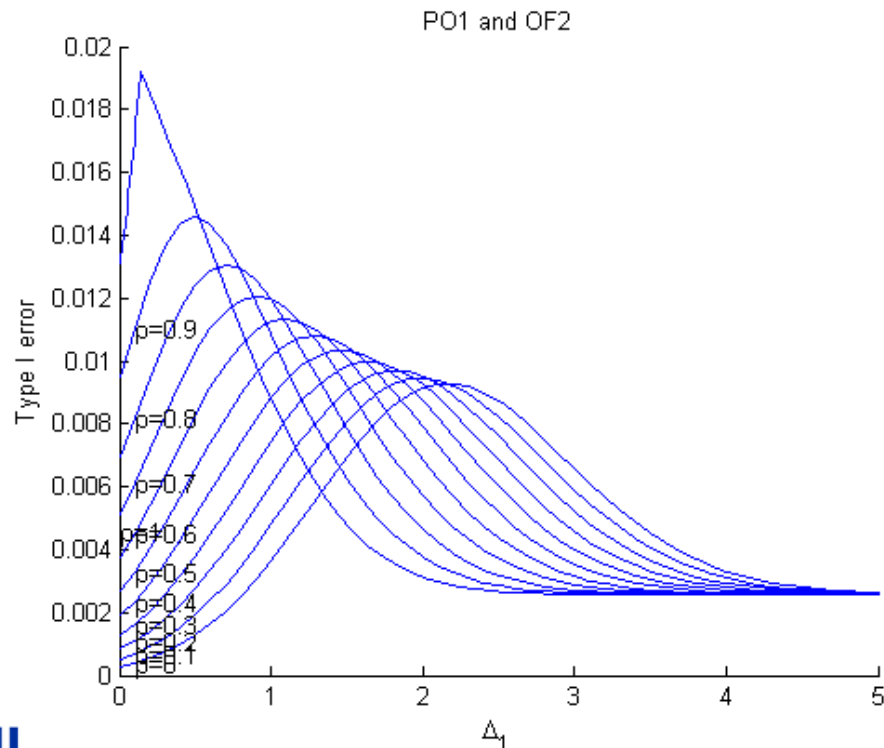
**FWER with  $(c_1 = 1.98\sqrt{2}, c_2 = 1.98)$ , and  $(d_1 = 1.98\sqrt{2}, d_2 = 1.98)$**



**FWER with  $(c_1 = 1.98\sqrt{2}, c_2 = 1.98)$ , and  $(d_1 = d_2 = 2.18)$**



## FWER with $(c_1 = c_2 = 2.18)$ , and $(d_1 = 1.98\sqrt{2}, d_2 = 1.98)$



## Review what we have learned

- The FWER depends on  $\rho$  and  $\Delta_1 = \delta_1\sqrt{n_1}$ , both of which are unknown; denote it by  $\text{FWER}(\Delta_1, \rho)$
- For fixed  $\rho$ , let  $\text{FWER}(\Delta_1^*(\rho), \rho) = \max_{\Delta_1} \text{FWER}(\Delta_1, \rho)$ 
  - $\text{FWER}(\Delta_1^*(\rho), \rho)$  increases with  $\rho$
  - Worst-case FWER occurs at  $\text{FWER}(\Delta_1^*(1), 1)$
- If  $(c_1, c_2)$  are level- $\alpha$  primary boundaries and  $(d_1, d_2)$  are level- $\alpha$  secondary boundaries then

$$\text{FWER}(\Delta_1^*(1), 1) = \alpha \text{ if } c_1 > d_1, c_2 < d_2$$

$$\text{FWER}(\Delta_1^*(1), 1) < \alpha \text{ if } c_1 < d_1, c_2 > d_2$$

In either case preservation of  $\text{FWER} \leq \alpha$  is guaranteed

# Why do we cater to worst case?

- We design for the worst case,  $\rho = 1$ , because  $\rho$  is unknown
- But suppose  $\rho$  were known. Then, for the case  
 $c_1 = 1.98\sqrt{2}$ ,  $c_2 = 1.98$  (level-0.025 OF boundary for primary bdy)  
 $d_1 = 2.18$ ,  $d_2 = 2.18$  (level-0.025 PO boundary for secondary bdy)  
the FWER is tabulated below as a function of  $\rho$

| $\rho$                                | 1     | 0.8   | 0.6   | 0.4   |
|---------------------------------------|-------|-------|-------|-------|
| $\text{FWER}(\Delta_1^*(\rho), \rho)$ | 0.025 | 0.019 | 0.017 | 0.016 |

- If  $\rho < 1$ , then  $\text{FWER}(\Delta_1^*(\rho), \rho) < 0.025$ . Therefore we can generate a more liberal secondary boundary ( $d_1 = d_2 < 2.18$ ) such that  $\text{FWER}(\Delta_1^*(\rho), \rho) = 0.025$

## Example: suppose we knew for a fact that $\rho = 0.8$

- If  $\rho = 0.8$ , then  $\text{FWER}(\Delta_1^*(0.8), 0.8) = 0.019$  at  $d_1 = d_2 = 2.18$ .  
There still remains some alpha ( $0.025 - 0.019 = 0.006$ ) to be utilized
- We may go on decreasing  $d_1$  and  $d_2$  until we exhaust all available alpha so that  $\text{FWER}(\Delta_1^*(0.8), 0.8) = 0.025$
- This occurs at  $d_1 = d_2 = 2.07$  which is a level-0.032 Pocock boundary
- By increasing the level of the Pocock boundary for the secondary endpoint from 0.025 to 0.032, we have increased overall power
- However, it is unrealistic to assume that  $\rho$  is known with certainty

# Estimate $\rho^*$ from the stage 1 data

- Obtain  $100 \times (1 - \epsilon)$  upper bound for  $\rho$ , say  $\rho^*$
- Suppose  $(\Delta_1^{(0)}, \rho^{(0)})$  are the true (unknown) values of  $(\Delta_1, \rho)$ . Then we can show that

$$\text{FWER}(\Delta_1^{(0)}, \rho^{(0)}) < \text{FWER}(\Delta_1^*(\rho^*), \rho^*) \times (1 - \epsilon) + \epsilon$$

- The FWER will be preserved at level  $\alpha$  if we select secondary boundaries  $(d_1, d_2)$  which are such that

$$\text{FWER}(\Delta_1^*(\rho^*), \rho^*) \times (1 - \epsilon) + \epsilon = \alpha$$

- If  $\rho^* < 1$ , the secondary boundaries  $(d_1, d_2)$  can have type-1 error greater than  $\alpha$

## Some Results

OF primary boundary at level-0.025:  $c_1 = 1.98\sqrt{2}$ ,  $c_2 = 1.98$

| Allowable Error for PO Secondary Boundary given $\rho^*$ |            |       |          |       |             |         |       |
|--|------------|-------|----------|-------|-------------|---------|-------|
| $\rho^*$   | Boundaries |       | P-Values |       | Error Spent |         |       |
|  | $d_1$      | $d_2$ | $p_1$    | $p_2$ | Stage 1     | Stage 2 | Total |
| 1  | 2.18       | 2.18  | 0.015    | 0.015 | 0.015       | 0.010   | 0.025 |
| 0.8  | 2.08       | 2.08  | 0.019    | 0.019 | 0.019       | 0.013   | 0.032 |
| 0.6  | 2.04       | 2.04  | 0.021    | 0.021 | 0.021       | 0.014   | 0.035 |
| 0.4  | 2.01       | 2.01  | 0.022    | 0.022 | 0.022       | 0.015   | 0.037 |

$\rho^*$  is the 99.9% upper confidence bound on  $\rho$

# Revisit the CAPTURE example

If sponsor wants secondary indication included in product label, he must **pre-specify**  $\alpha$ -spending functions for **both** primary and secondary endpoints

- **Conservative Strategy:** pre-specify level-0.025 OF spending function for primary endpoint and level-0.025 OF spending function for secondary endpoint
- **Aggressive Strategy:** pre-specify level-0.025 OF spending function for primary endpoint and level-0.025 PO spending function for secondary endpoint

Table 1: Interim Results and Boundaries Under Conservative Strategy (OF1-OF2)

| Endpoint  | Event Rates  |              | Interim Test Statistic | Stopping Boundaries |              |
|-----------|--------------|--------------|------------------------|---------------------|--------------|
|           | Placebo      | Abciximab    |                        | Interim             | Final        |
| Primary   | 84/532 (16%) | 55/518 (11%) | $X_1 = 2.49$           | $c_1 = 2.34$        | $c_2 = 2.01$ |
| Secondary | 44/532 (8%)  | 26/518 (5%)  | $Y_1 = 2.12$           | $d_1 = 2.34$        | $d_2 = 2.01$ |

Table 2: Interim Results and Boundaries for CAPTURE Under Strategy 2 (Aggressive)

| Endpoint  | Event Rates  |              | Test Statistic | Stopping Boundaries |              |
|-----------|--------------|--------------|----------------|---------------------|--------------|
|           | Placebo      | Abciximab    |                | Interim             | Final        |
| Primary   | 84/532 (16%) | 55/518 (11%) | $X_1 = 2.49$   | $c_1 = 2.34$        | $c_2 = 2.01$ |
| Secondary | 44/532 (8%)  | 26/518 (5%)  | $Y_1 = 2.12$   | $d_1 = 2.04$        | $d_2 = 2.26$ |

**In this situation, the aggressive strategy would have paid off**

# Concluding Remarks

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- Primary endpoint boundaries  $(c_1, c_2)$  must be **level- $\alpha$**
- Cannot use  $d_1 = d_2 = z_\alpha$  for secondary endpoint
- Any choice of **level- $\alpha$**  boundaries  $(d_1, d_2)$  for secondary endpoint will guarantee  $\text{FWER} \leq \alpha$
- Under certain conditions, it is possible to use secondary boundaries  $(d_1, d_2)$  **whose level exceeds  $\alpha$** 
  1. If  $c_1 < d_1$  and  $c_2 > d_2$
  2. If we replace  $\rho$  by its  $100 \times (1 - \epsilon)$  upper bound  $\rho^*$
- **Secondary boundaries at a level that exceeds  $\alpha$  are likely to face regulatory obstacles despite their statistical validity**

# Related References

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1. Glimm E, Maurer, Bretz (2010). Hierarchical testing of multiple endpoints in group-sequential trials. *Statistics in Medicine*, **29**, 219-228.
2. Hung HJM, Wang S-J, O'Neill R (2007). Statistical considerations for testing multiple endpoints in group sequential or adaptive clinical trials. *J. Biopharm. Statist.*, **17**: 1201-1210.
3. Tamhane AC, Mehta CR, Liu L (2010). Testing a primary and a secondary endpoint in a group sequential design. *Biometrics* (in press).
4. The CAPTURE Investigators (1997). Randomized placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina. *Lancet*, **349**, 1429-1435.