Hierarchical testing in a group sequential design with different information times

Dong Xi, Novartis

Jiangtao Gou, Hunter College of CUNY

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Agenda

- Background on hierarchical testing and group sequential design
- Refined boundary with different information times
- Clinical trial application
- Other types of hierarchical testing in group sequential design
- Conclusion

Hierarchical testing

- In confirmatory trials, hierarchical testing is commonly used to control the familywise error rate at level α
- For many oncology trials
  - Primary endpoint (PE): PFS
  - Secondary endpoint (SE): OS
  - Or the other way round (PE: OS and SE: PFS)
- First test PE at level α
- If significant, test SE at level α; if not significant, stop testing

Group sequential design

- Allow interim monitoring along the course of a trial
- Possible early stopping due to overwhelming benefit
  - Test the hypothesis with 50% and 100% of the planned number of patients/events
  - At any analysis, if the hypothesis is rejected, claim success
- Potentially save time to make efficacious treatment available to patients
- Due to repeated testing of the same hypothesis with accumulating data, the test has to be adjusted for Type I error control

Group sequential design

- Consider a group sequential design for testing H_0: $\theta \leq 0$ against H_a: $\theta > 0$ with an interim and a final analysis
  - E.g, $\theta = -\log HR$
- Interim analysis is planned at information time t $(0 < t < 1)$
- t: information fraction at the interim analysis

$$= \frac{\text{information at the interim analysis}}{\text{information at the final analysis}}$$

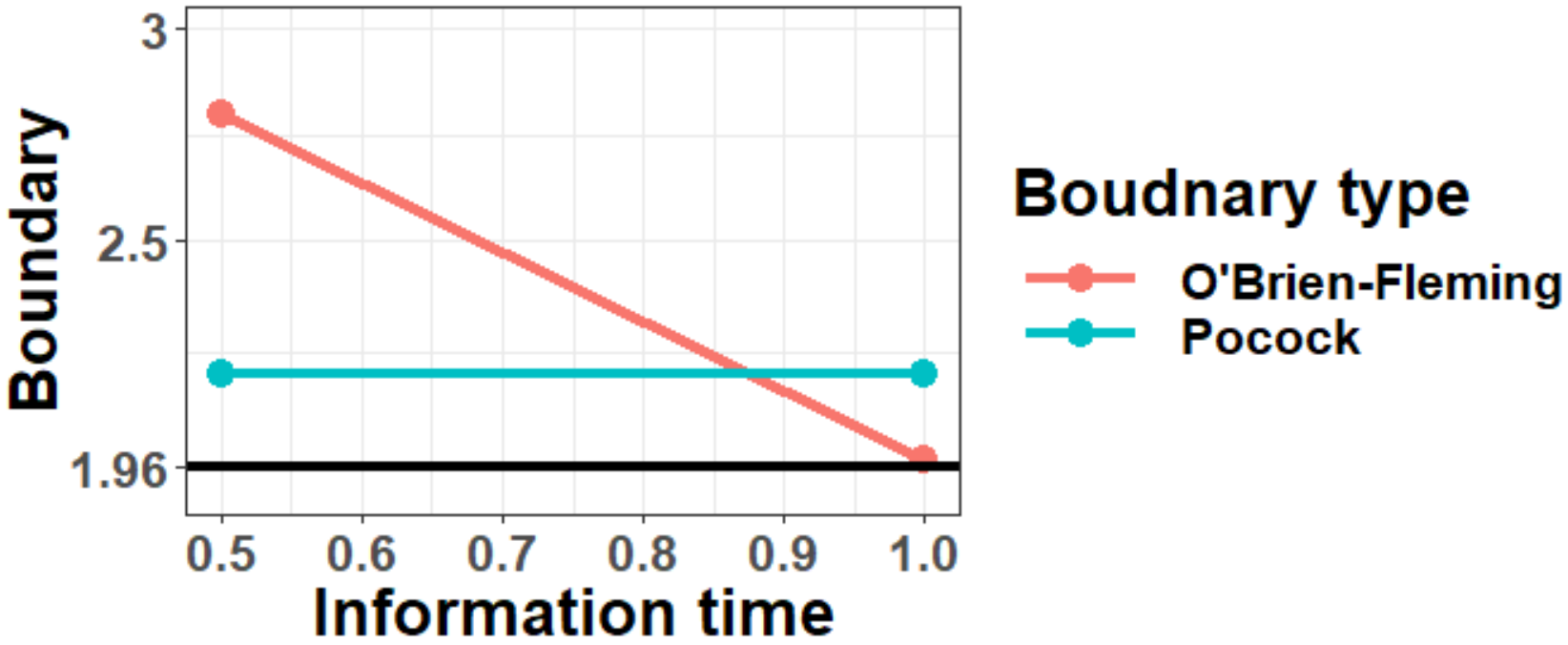
- Information: inverse of the variance of the estimates
  - Normal endpoint: proportional to the sample size
  - Survival endpoint: proportional to the number of events
- E.g., a group sequential design tests the null hypothesis twice: at 50% sample size or number of events and at 100%

Group sequential design

- Z_1 and Z_2 are test statistics at the interim and final analyses, respectively
  - E.g, Log-rank test statistics with t information and 100% information
- Under H_0, Z_1 and Z_2 follow a bivariate normal distribution with mean 0, variance 1, and correlation $\sqrt{t}$
- H_0 is rejected if $Z_1 \geq c_1$ or $Z_2 \geq c_2$
- We need to find boundary c_1 and c_2 such that
  $P(Z_1 \geq c_1 \text{ or } Z_2 \geq c_2) = 1 - P(Z_1 < c_1, Z_2 < c_2) = \alpha$

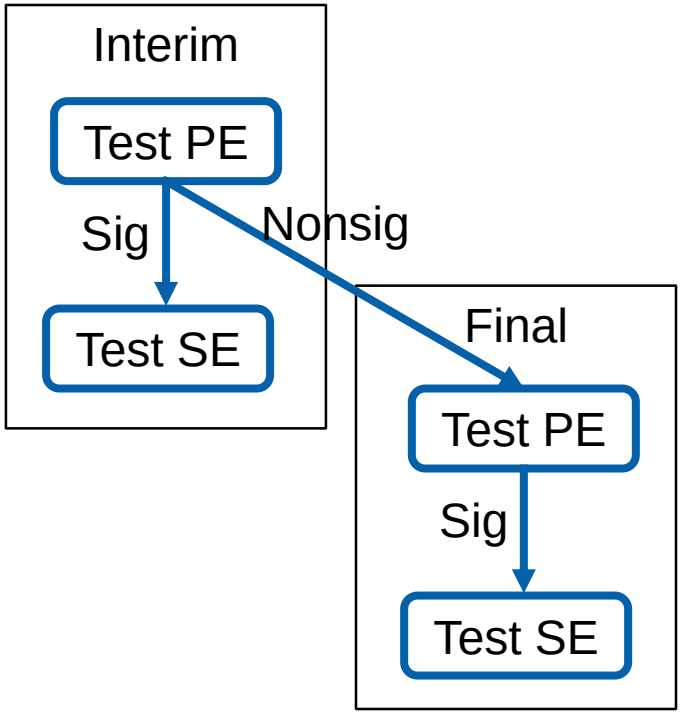
Two group sequential designs

- O'Brien-Fleming boundary: $c_1 = c_2/\sqrt{t}$
  - $\alpha = 0.025$, $t = 0.5$, $c_1 = 2.797$, $c_2 = 1.977$ compared with $z_{1-\alpha} = 1.96$
- Pocock boundary: $c_1 = c_2$
  - $\alpha = 0.025$, $t = 0.5$, $c_1 = c_2 = 2.178$ compared with $z_{1-\alpha} = 1.96$



Clinical trial example

- CheckMate 025 is a Phase 3 trial comparing nivolumab against everolimus in patients with renal-cell carcinoma (Motzer et al. 2015)
  - PE: OS
  - SE: PFS
- An interim analysis is scheduled at $t_p = 0.7$ for PE using O'Brien-Fleming boundary



At what level should we test PE and SE at interim and final?

For PE, use α-level group sequential boundary

Analysis	Boundary (information)	
	PE using O'Brien-Fleming	SE
Interim	2.4 ($t_p = 0.7$)	?
Final	2.008	?

- At interim with 70% PE events, reject H_{p0} if $Z_{p1} \geq 2.4$
- At final, reject H_{p0} if $Z_{p2} \geq 2.008$
- Since PE can only be rejected at either interim or final, there is only one chance to test SE
  - Can SE be tested at level α whenever PE is significant?

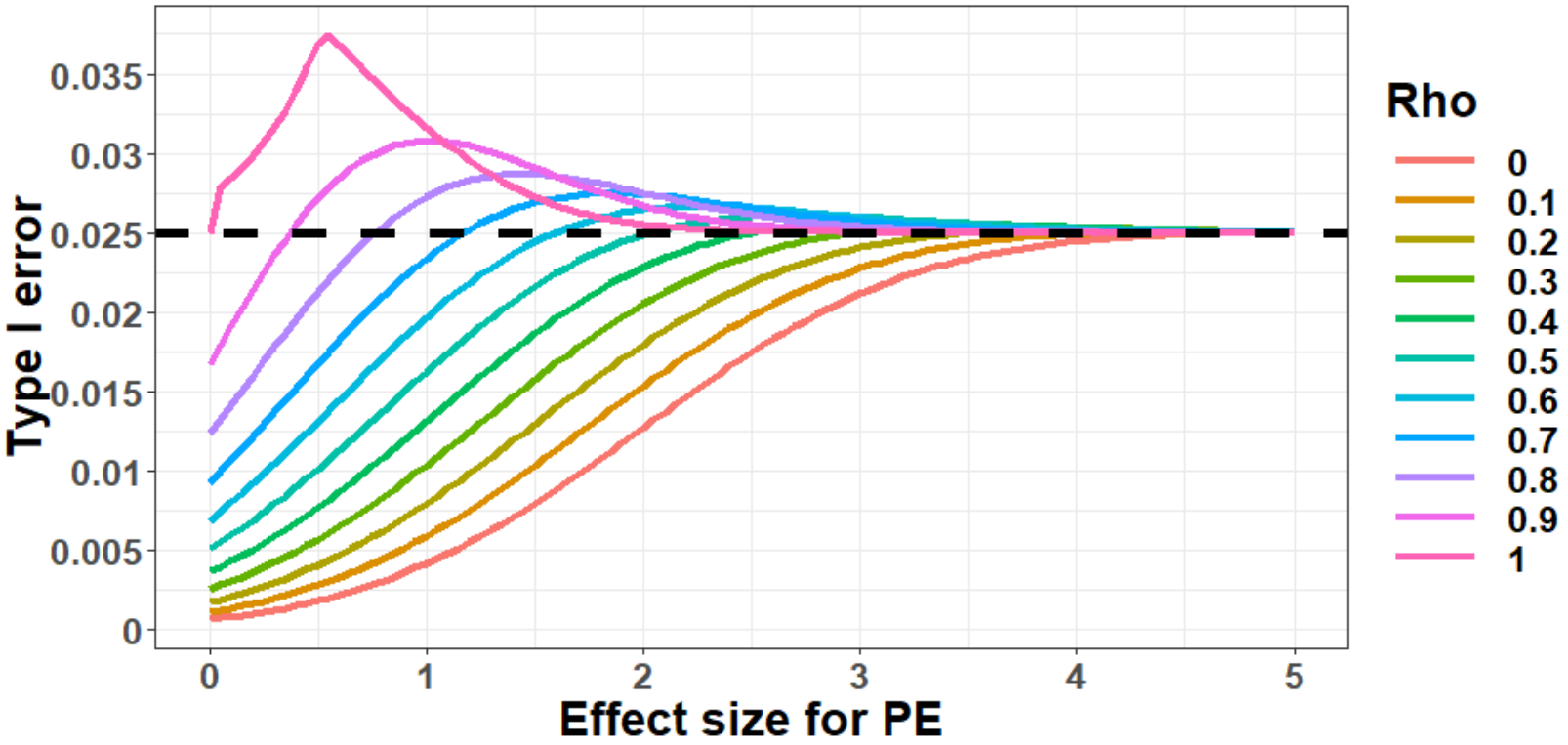
Literature review

- Although SE is tested only once, testing it at level α will inflate Type I error (Hung, Wang, O'Neil, 1997)
- Type I error inflation depends on ρ, the correlation between PE and SE (Tamhane, Mehta, Liu, 2010; Glimm, Maurer, Bretz, 2010)
- Test PE using the O'Brien-Fleming boundary at level α
  - $c_1 = 2.4$ and $c_2 = 2.008$
- Type I error
  - Rejecting SE when PE is false but SE is true
  - $P(Z_{p1} \geq c_1, Z_{s1} \geq d_1) + P(Z_{p1} < c_1, Z_{p2} \geq c_2, Z_{s2} \geq d_2)$

Reject SE at interim

Reject SE at final

Type I error inflation for SE tested at level $\alpha = 0.025$ $(d = 1.96)$ whenever PE is significant



- When $\rho = 0$, Type I error is controlled
- When $\rho > 0$, the maximum inflation increases with ρ

Solution

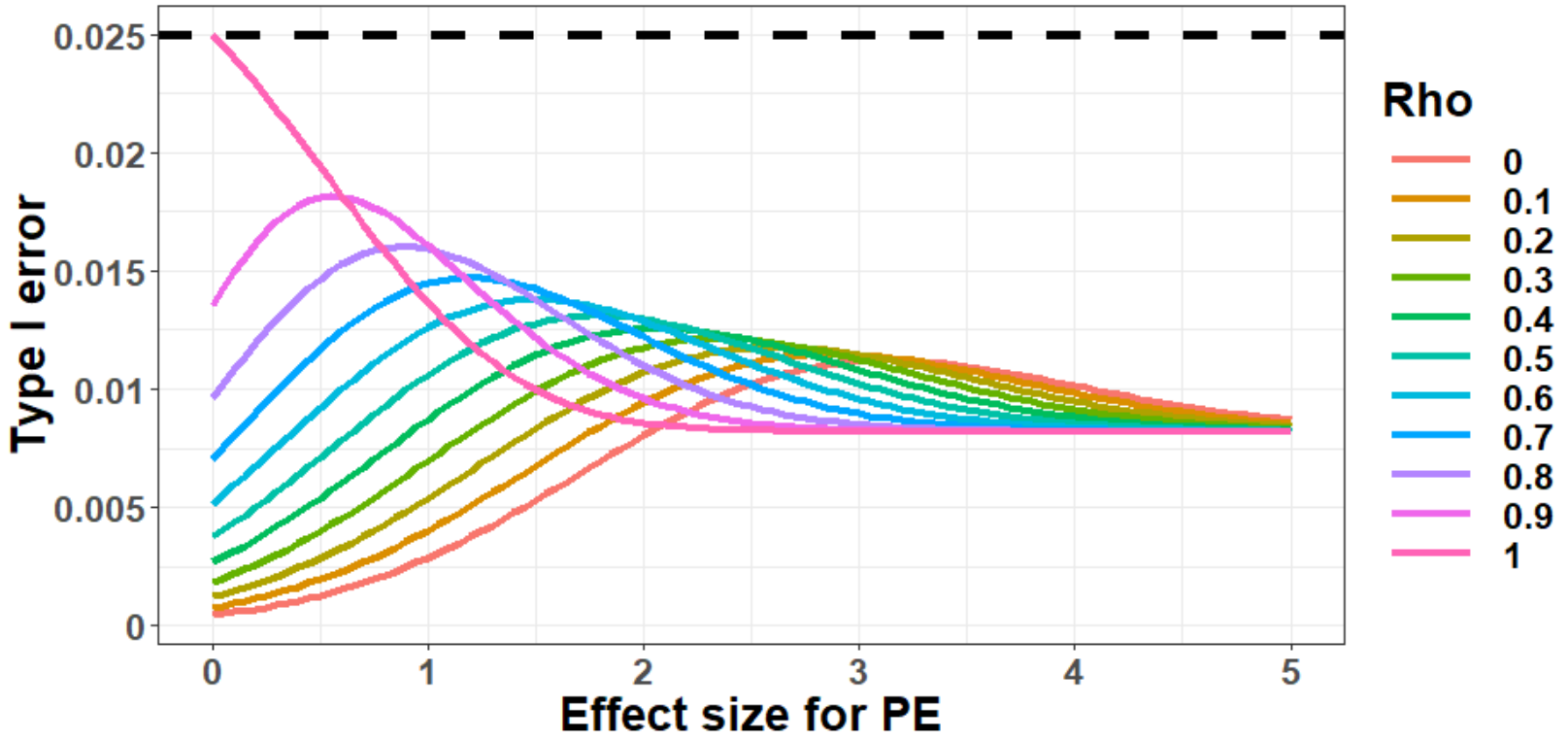
(Tamhane, Mehta, Liu, 2010; Glimm, Maurer, Bretz, 2010)

- Group sequential design has to be used for SE

Analysis	Boundary (information)	
	PE using O'Brien-Fleming	SE using O'Brien-Fleming
Interim	2.4 ($t_p = 0.7$)	2.4 ($t_s = 0.7$)
Final	2.008	2.008

- At interim with 70% PE events, reject H_{p0} if $Z_{p1} \geq 2.4$
  - If H_{p0} rejected, reject H_{s0} if $Z_{s1} \geq 2.4$
- If H_{p0} not rejected at interim, reject H_{p0} at final if $Z_{p2} \geq 2.008$
  - If H_{p0} rejected, reject H_{s0} if $Z_{s2} \geq 2.008$

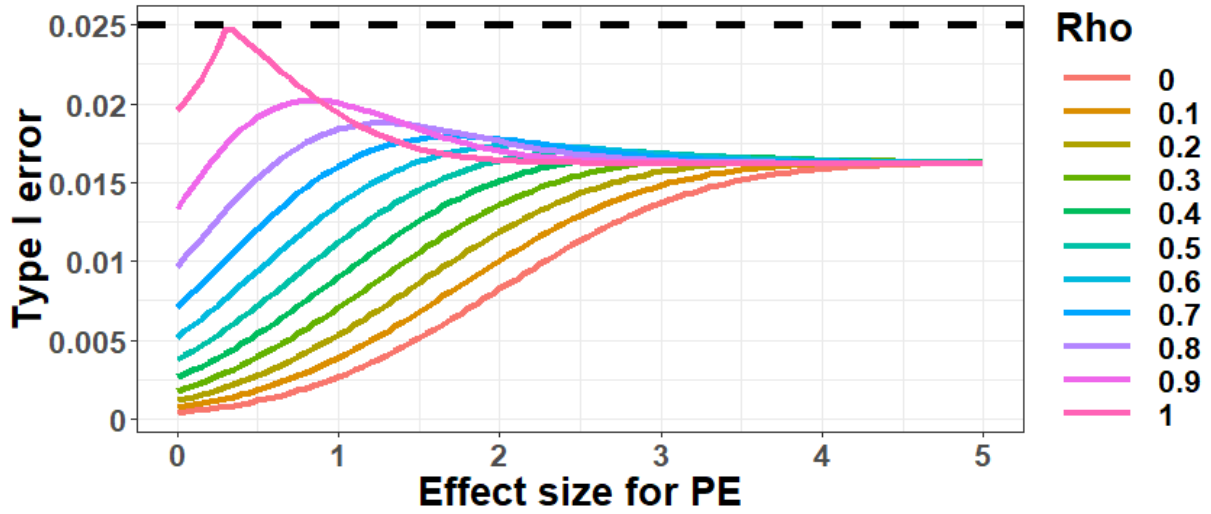
Type I error control for SE tested at level $\alpha = 0.025$ using O'Brien-Fleming boundary



- O'Brien-Fleming boundary for PE and SE: (2.4, 2.008)
- When $\rho = 1$, Type I error achieves 0.025 under H_{p0}
- Usually don't know the truth about ρ. Be conservative with $\rho = 1$

Group sequential design for SE can be different from the group sequential design for PE

Analysis	Boundary (information)	
	PE using O'Brien-Fleming	SE using Pocock
Interim	2.4 ($t_p = 0.7$)	2.139 ($t_s = 0.7$)
Final	2.008	2.139



– O'Brien-Fleming for PE and Pocock for SE may have power advantages (Glimm, Maurer, Bretz, 2010)

SE may have a different information time from PE

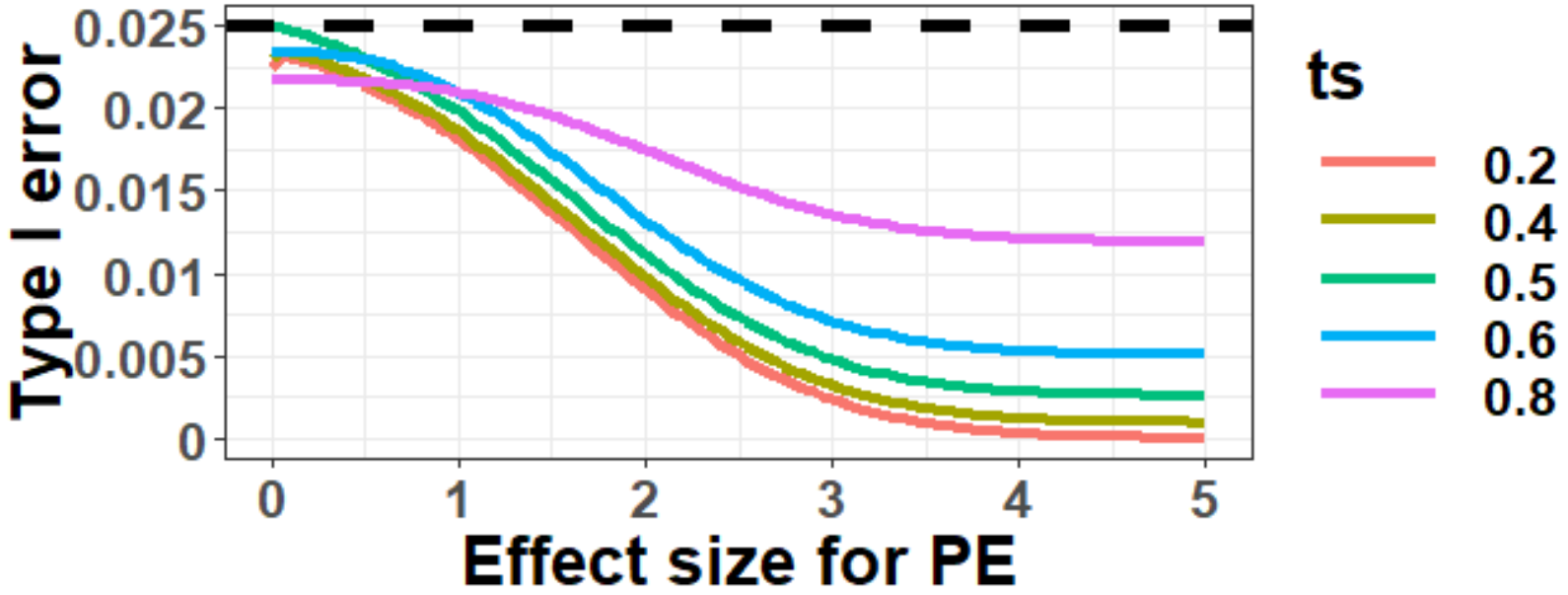
- As a result of group sequential design for SE, we need to pre-specify the information time for SE at the interim
  - Information time for SE is random at the interim, depending on PE
  - But we need to give a best guess; otherwise, it would be difficult to justify any post-hoc boundary for SE after PE is significant
- SE has the same critical values of PE only if both
  - the same type of boundary is used and
  - $\boldsymbol{t_p = t_s}$
- What if the information time for SE is different from the information time for PE?

Question of interest

- Past results in the literature assume that the information time is the same for PE and SE at the interim
- However, this is unlikely to be the case for trials with time to event endpoints
  - PFS takes less time to accumulate than OS
  - At the interim, PFS may have a larger information time
- For a trial including non-inferiority and superiority objectives, the analysis sets may be different
- Do we have to use a group sequential design for SE in order to control Type I error?
  - It depends on the difference of information times between PE and SE

Type I error when information time is different

- At interim, assume $t_p = 0.5$ but $t_s = 0.2, 0.4, 0.5, 0.6, 0.8$
- PE and SE are tested using the O'Brien-Fleming boundary



- When $t_s = 0.5$, the maximum Type I error is 0.025
- When $t_s \neq 0.5$, the maximum Type I error is < 0.025

Why

- When the information time is different for PE and SE, the correlation structure changes
- At interim,

$$Corr\left(Z_{p1}, Z_{s1}\right) = \rho \sqrt{\frac{\min\left(t_p, t_s\right)}{\max\left(t_p, t_s\right)}}$$

- The correlation depends on how much t_p and t_s overlap
  - In the normal setting, assume t_p patients have PE measurements and t_s patients have SE measurements
  - The correlation is generated from the $\min\left(t_p, t_s\right)$ patients who have both measurements

Refined boundary

- When the information time is different for PE and SE, we can refine the group sequential boundary for SE
  - Refined boundary: uniformly less conservative boundary
- Idea for refinement: lower the usual α-level boundary for SE until the actual Type I error is exactly α
- Select α-level boundary for PE (c_1, c_2)
- Solve for the boundary for SE (d_1, d_2) such that the Type I error is controlled exactly at level α

$$P\left(Z_{p1} \geq c_1, Z_{s1} \geq d_1\right) + P\left(Z_{p1} < c_1, Z_{p2} \geq c_2, Z_{s2} \geq d_2\right) = \alpha$$

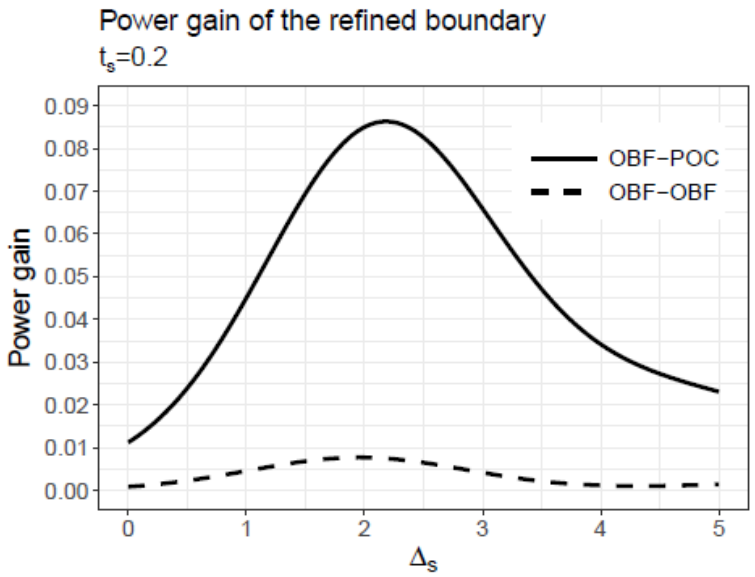
Reject SE at interim

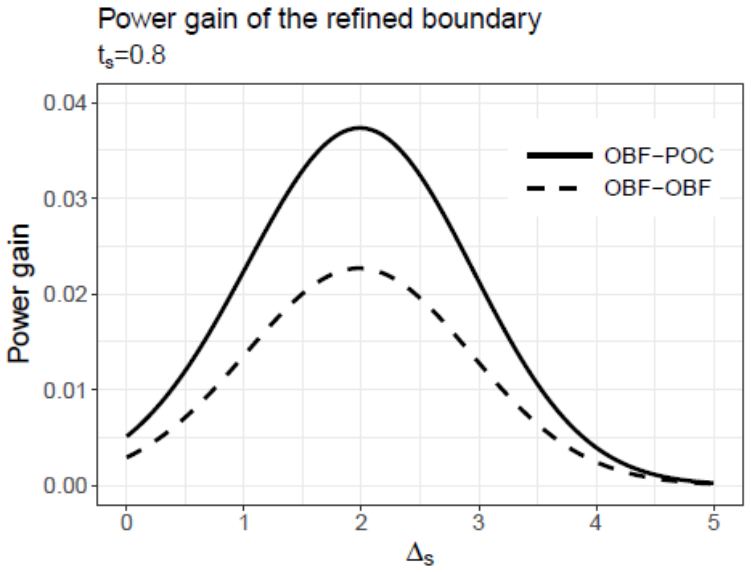
Reject SE at final

Refined boundary examples

- The more different t_p and t_s are, the more refinement achieved (or the less conservative the boundary is)
- When $t_p = 0.5$ and $t_s = 0.2$, SE can be tested at level α at interim or final, whenever PE is significant
  - No group sequential adjustment is needed for SE
- When $t_p = 0.5$ and $t_s = 0.8$
  - Usual α-level O'Brien-Fleming boundary is $(2.260, 2.021)$
  - Refined boundary is $(2.193, 1.962)$

Power gain (refined vs. usual α-level)





- When $t_p = 0.5$ and $t_s = 0.2$, the power gain is ~9% if Pocock boundary for SE and very little if O'Brien-Fleming boundary for SE
- When $t_p = 0.5$ and $t_s = 0.8$, the power gain is ~4% if Pocock boundary for SE and ~2% if O'Brien-Fleming boundary for SE

Application to CheckMate 025
PE: OS and SE: PFS

- An interim analysis is scheduled at $t_p = 0.7$ for PE using O'Brien-Fleming Lan-DeMets boundary
  - Assume that $t_s = 0.8$ for SE at interim
- α-level boundary using the spending function
  - PE: $(2.4, 2.008)$ and SE: $(2.251, 2.025)$
- Solve the following equations simultaneously for (d_1, d_2)

$$P(Z_{s1} \geq d_1) = \varepsilon(y, t_s = 0.8)$$

$$P(Z_{s1} < d_1, Z_{s2} \geq d_2) = y - \varepsilon(y, t_s = 0.8)$$

ε: Lan-DeMets spending function

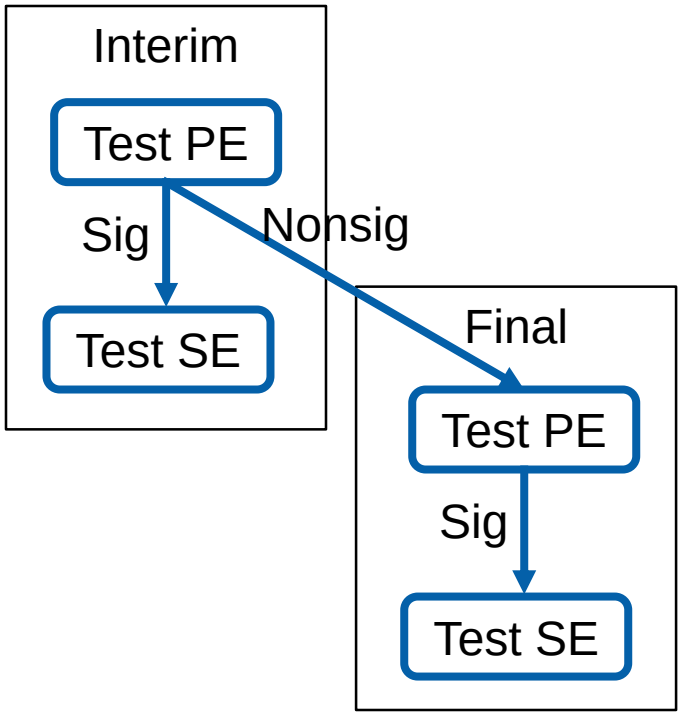
$$P(Z_{p1} \geq 2.438, Z_{s1} \geq d_1) + P(Z_{p1} < 2.438, Z_{p2} \geq 2, Z_{s2} \geq d_2) = 0.025$$

Type I error control

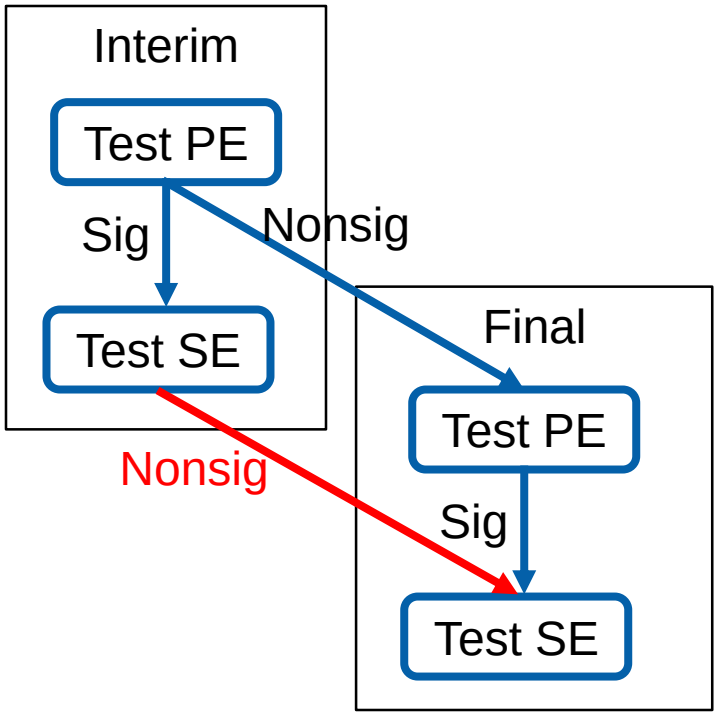
- Refined boundary for SE: $(2.192, 1.975)$

Other types of hierarchical testing in group sequential design

Previous:
Stagewise hierarchical



Overall hierarchical

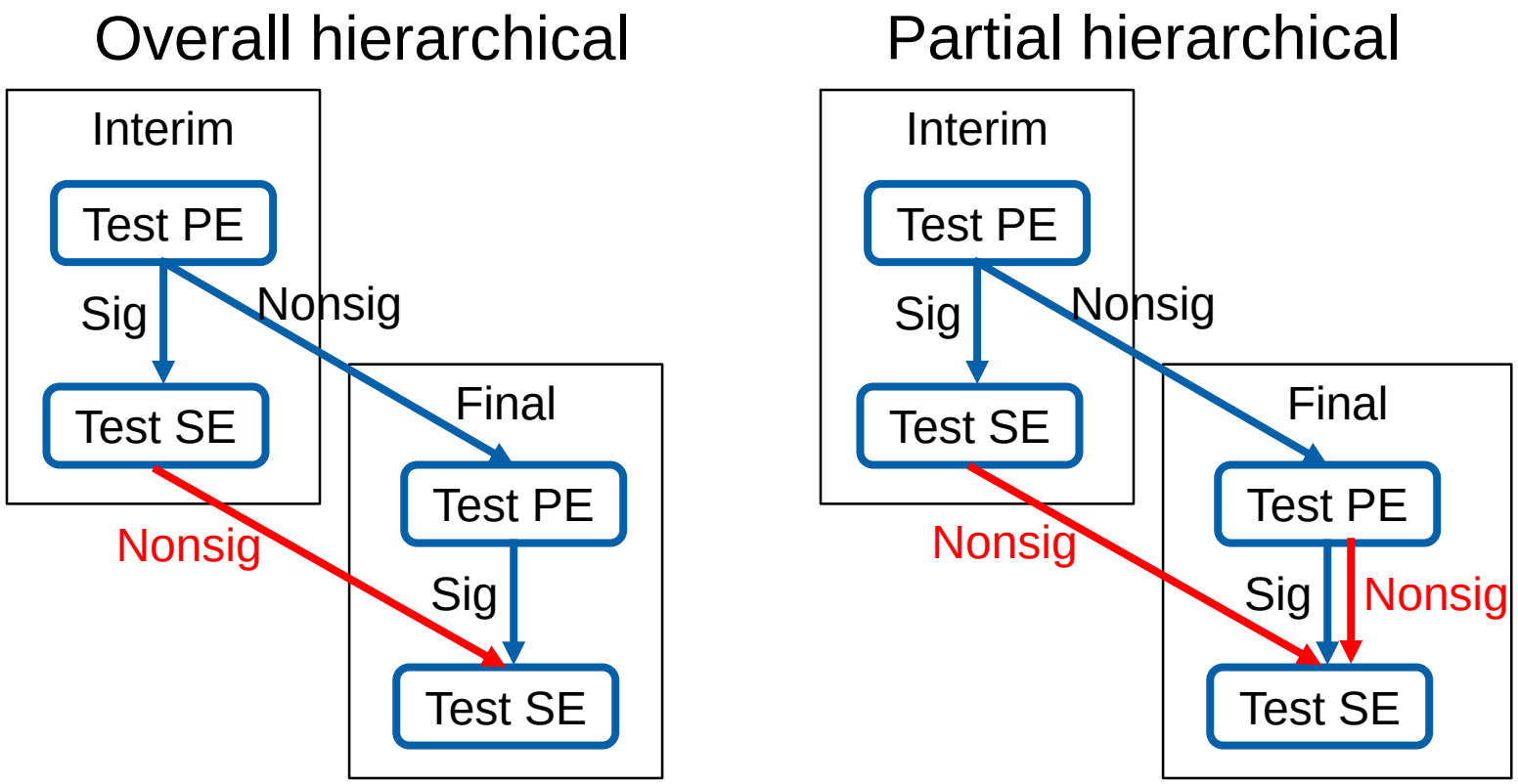


Glimm, Maurer, Bretz, 2010

Overall hierarchical

- When PE is significant at interim, test SE at its interim and final analyses, if not significant earlier
  - PE: PFS
  - SE: OS
- If the true effect on PE is very positive, PE is almost always significant
- SE is always tested at interim and final analyses, if not significant earlier
- α-level group sequential design is required for SE to control Type I erro at level α

Other types of hierarchical testing in group sequential design



Glimm, Maurer, Bretz, 2010

Partial hierarchical

- When PE is not significant at interim, test both PE and SE at final analysis simultaneously
- If PE: PFS is not significant at interim, the clinical team may want to preserve a small chance to reject SE: OS, even if PFS is not significant at all
- Hierarchical at interim but not at final
- May need to split α between PE and SE

Partial hierarchical example

Analysis 1: PFS final and OS interim
Analysis 2: OS final

- PFS is only tested once (i.e., no PFS interim analysis)
- OS can be tested at
  - OS interim, only if PFS significant
  - OS final, regardless of PFS

- If PFS is tested at level α, then OS can only be test at OS interim at level α, if PFS significant
- Any possibility to reject OS at the final analysis will inflate Type I error

- If PFS is tested at level $\alpha/2$, then OS can be test at OS interim and final
- Refined boundary for SE is (2.129, 2.237) when $t_s = 0.5$
- Less conservative than testing OS at level $\alpha/2$
  - O'Brien-Fleming (3.183, 2.251)
  - Pocock (2.450, 2.450)

Conclusions

- Different strategies to design hierarchical testing in group sequential design
- In stagewise hierarchical testing (PE: OS, SE: PFS), refinement with less conservative boundary for SE is possible when the information time is different from PE
- In overall hierarchical testing (PE: PFS, SE: OS), refinement is not needed for two stage testing
  - For more than two stages, refinement is possible (Tamhane et al., 2018)
- In partial hierarchical testing (PE:PFS, SE: OS), refinement is also possible for SE

Reference

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- R package: gsrsb

Thank you

dong.xi@novartis.com