Overall Type I Error Control for Seamless Phase II/III Adaptive Design using Biomarkers

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Outline

- Background
- Alternative Methods to Adjust Phase II p-Value
  - Theoretical Results for Correlation Matrix of Test Statistics
  - Simulations for Overall Type I Error
- Conclusion
  - Both Rank-based Sidák/Dunnett adjustment can control type I error rate.
  - Rank-based Dunnett adjustment is less conservative (and more powerful) than rank-based Sidák adjustment.

Background

- To accelerate clinical development, seamless II/III adaptive design is a popular strategy to combine phase II dose selection with phase III confirmatory objectives.
- Phase III optimal dose shifted from MTD to MED for oncology drug (FDA Project Optimus) requires gathering more data on candidate doses to inform phase III dose selection.
- Combing phase II and phase III efficacy endpoint without multiplicity adjustment will cause type I error inflation.
- Sidák adjustment is overly conservative. And it also doesn't account for scenarios when dose selected is not the best in biomarker response.
- **Two biomarker rank-based approaches are proposed for overall type I error control that accounts for the underlying correlation between test-statistics across doses and the rank of biomarker response.**

Seamless II/III Adaptive Design Using Biomarker

Example: Merck second-generation Human Papilloma Virus (HPV) vaccine trial. (Li, etc. 2019)

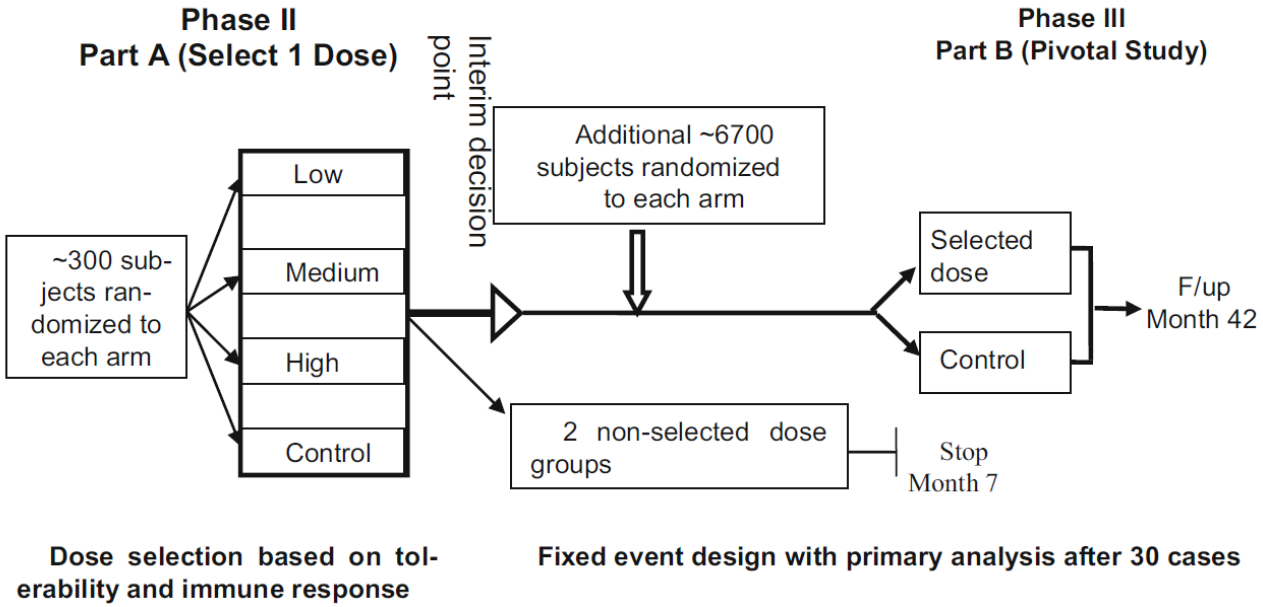

Fig. 1 Seamless phase II/III design with dose-selection for the HPV vaccine trial

Interim decision rule: A dose was selected based on the immunogenicity and tolerability results from phase II (efficacy endpoint remained blinded) and continued into phase III.

Seamless II/III Adaptive Design Using Biomarker

Potential Advantages

- limiting patient exposure to unsafe or ineffective treatments
- Savings of trial resources
- accelerating the development process while ensuring that the adaptive clinical trials can provide the evidence for regulatory decision making

Potential Disadvantage: Type I error inflation

- A potential type I error inflation for the final efficacy analysis using aggregated phase II and III data might arise due to various reasons such as
  - the correlation between the biomarker and the efficacy endpoint
  - the number of dose groups to choose from
  - the decision rules for dose selection

Combined Test – Cont. (Li, etc. 2019)

Incorporate this procedure into seamless phase II/III design with dose selection step by step:

- Step 1: Compute the p-value $\boldsymbol{p_{0,s}}$ testing the difference between the selected treatment group and the control group regarding the efficacy endpoint for the population enrolled in phase II.

- Step 2: Conduct the multiplicity adjustment by the Sidák test and compute the first-stage (phase II)-adjusted p-value as follows:

$$\boldsymbol{p_1 = 1 - \left(1 - p_{0,s}\right)^m},$$

where m is the number of treatment groups at phase II.

- Step 3: Combine the p-values obtained from both phases:

$$\boldsymbol{p = C(p_1, p_2) = 1 - \Phi\left(\sqrt{w_1}\Phi^{-1}(1 - p_1) + \sqrt{1 - w_1}\Phi^{-1}(1 - p_2)\right)},$$

Where p_2 is the p-value for the efficacy endpoint in phase III, $\boldsymbol{\Phi(\cdot)}$ is the cumulative distribution function of the standard normal distribution, w_1 is the weight set for phase II. Li. etc. used $w_1 = \frac{N_1}{N_1+N_2}$, where N_1 and N_2 are the sample sizes on the selected dose or control group in phase II and III, respectively.

- Step 4: Compare the combined $\boldsymbol{p}$ value with the prespecified error level $\boldsymbol{\alpha}$.

Alternative Methods to Adjust Phase II p-value

Rank-based selection: The dose with the best response may have safety issues and is not always selected to continue into phase III.

r: the rank of a biomarker test statistics, higher rank indicates better response

❖ Rank-based Sidák adjustment

- Obtain p-value p_1 using rank-based Sidák adjustment
  - $\boldsymbol{p_1 = 1 - (1 - p_{0,s})^1 = p_{0,s}}$: No penalty.
  - $\boldsymbol{p_1 = 1 - (1 - p_{0,s})^r}$: Implement penalty based on rank.
  - $\boldsymbol{p_1 = 1 - (1 - p_{0,s})^m}$: Maximum penalty, best response.

❖ Rank-based Dunnett adjustment

- Obtain p-value p_1 using rank-based Dunnett adjustment, under normal approximation.
  - Apply Dunnett adjustment similarly to rank-based Sidák adjustment.

Simulation for Type I Error Rate

- Simulate test statistics from Multivariate normal distribution under null hypotheses
- Consider 3 doses vs. placebo in phase II, balanced design
- $\rho_1 = 0.5$ be correlation coefficient compared to common control;
- ρ_2 be the correlation coefficient between biomarker and efficacy endpoint, which varies from 0 to 1 by step 0.1;
- $B = 500{,}000$ be the number of simulations;
- $\alpha = 0.025$ be the significance level at final test;
- $w1 = 1/7$ be the weight of Phase II;
- Phase II dose selection based on totality of PK/PD, efficacy and safety;

❖ Phase II Type I error control methods

- Rank-based: ordered test stats for biomarkers Sidák and Dunnett:
  - 3 dose adjustment for max rank $r = 3$;
  - 2 dose adjustment for rank $r = 2$;
  - no adjustment for rank $r = 1$ ($\boldsymbol{p_1 = p_{0,s}}$).

Theoretical Results for coefficients - Cont.

$\boldsymbol{H_0}$: There is no difference between the j^{th} treatment and the control group for efficacy endpoint $(i = 1)$ or biomarker $(i = 2)$.

Test Statistics:

$$\boldsymbol{TS_{ij}} = \frac{\bar{\boldsymbol{y}}_{\boldsymbol{ij}} - \bar{\boldsymbol{y}}_{\boldsymbol{i0}}}{\sqrt{\boldsymbol{S^2}\left(\frac{\boldsymbol{1}}{\boldsymbol{n_j}} + \frac{\boldsymbol{1}}{\boldsymbol{n_0}}\right)}}, \qquad \boldsymbol{j = 1, 2, \cdots, m}$$

Where S^2 is the pooled variance, n_j and n_0 are the subjects involved in the j^{th} treatment and the control group respectively.

Theoretical Results for coefficients - Balanced Design

Example: Suppose $\rho = 0.8$, then the correlation matrix of test statistics for efficacy endpoints and biomarker is shown in table 1.

Table 1 Correlation Matrix of Test Statistics

Test Statistics		**Efficacy Test Statistic**			**Biomarker Test Statistic**		
		TS_{11}	TS_{12}	TS_{13}	TS_{21}	TS_{22}	TS_{23}
Efficacy Test Statistic	TS_{11}	1	0.5	0.5	0.8	0.4	0.4
	TS_{12}	0.5	1	0.5	0.4	0.8	0.4
	TS_{13}	0.5	0.5	1	0.4	0.4	0.8
Biomarker Test Statistic	TS_{21}	0.8	0.4	0.4	1	0.5	0.5
	TS_{22}	0.4	0.8	0.4	0.5	1	0.5
	TS_{23}	0.4	0.4	0.8	0.5	0.5	1

Biomarker Rank-based Sidák/Dunnet adjustment Simulation Results

Table 2 Comparison of Empirical Type I Error Rate

Correlation Biomarker & Efficacy	Empirical Type I Error Rate: Prob(obs. Final Combined p-value <0.025)				
	no adjustment for $r = 1$	Rank-based Sidák Adj. for $r = 2$	2-dose Dunnett Adj. for $r = 2$	Rank-based Sidák Adj. for $r = 3$	3-dose Dunnett Adj. for $r = 3$
$\rho_2 = 0.0$	0.02510	0.01561	0.01761	0.01133	0.01452
$\rho_2 = 0.1$	0.02325	0.01588	0.01711	0.01254	0.01523
$\rho_2 = 0.2$	0.02217	0.01533	0.01775	0.01321	0.01627
$\rho_2 = 0.3$	0.02148	0.01584	0.01738	0.01433	0.01689
$\rho_2 = 0.4$	0.01951	0.01513	0.01759	0.01532	0.01872
$\rho_2 = 0.5$	0.01860	0.01506	0.01862	0.01625	0.02082
$\rho_2 = 0.6$	0.01831	0.01495	0.01761	0.01750	0.02157
$\rho_2 = 0.7$	0.01711	0.01490	0.01676	0.01778	0.02239
$\rho_2 = 0.8$	0.01546	0.01468	0.01717	0.02002	0.02349
$\rho_2 = 0.9$	0.01478	0.01437	0.01654	0.02020	0.02379
$\rho_2 = 1.0$	0.01264	0.01347	0.01544	0.02071	0.02457

Conclusion

- Proposed (biomarker rank-based Sidák/Dunnett methods) accounted for the correlation between test statistics can control the type I error.
  - The theoretical correlations between test statistics of biomarker and efficacy endpoints are derived and used for the simulations.
  - The methods are demonstrated via simulations for correlations between biomarker and efficacy endpoint ranging from 0 to 1 with step=0.1.
- Rank-based Dunnett adjustment is less conservative (and more powerful) than rank-based Sidák adjustment.

Reference

[1] U.S. Food and Drug Administration, Oncology Center of Excellence (OCE) Project Optimus: Reforming the dose optimization and dose selection paradigm in oncology, https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus/ (accessed July 5, 2022).

[2] Pei Li, Yanli Zhao, Xiao Sun and Ivan S. F. Chan, Chapter 17 Multiplicity Adjustment in Seamless Phase II/III Adaptive Trials Using Biomarkers for Dose Selection.

[3] FDA Project Optimus, https://www.fda.gov/about-fda/oncology-center-excellence/project-optimus#:~:text=The%20goal%20of%20Project%20Optimus,or%20doses%20that%20maximizes%20not /(accessed July 15, 2022).

Questions?

Thank you!