Group Sequential Trial with a Biomarker Subpopulation

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Outline

- Motivation: Phase III PD-L1/PD-1 Monotherapy Studies
- Introduction: Multiplicity Adjustment in Oncology Trials
- Method: Complete Correlation Structure (CCS) Incorporating both GSD and Sub-Population
- Evaluation of CCS
- Implementation
- Discussion&Conclusion

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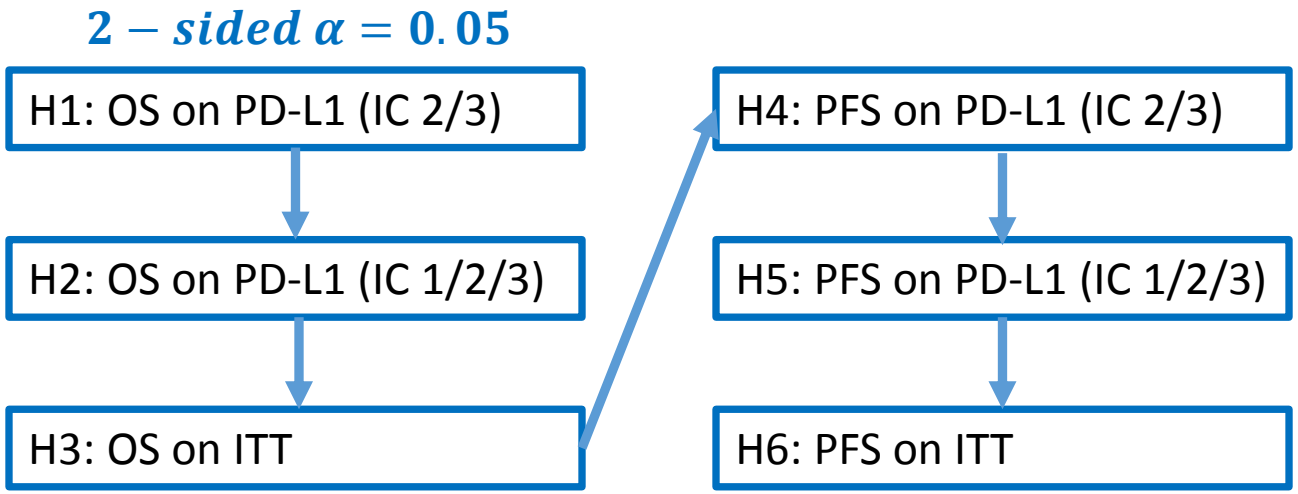
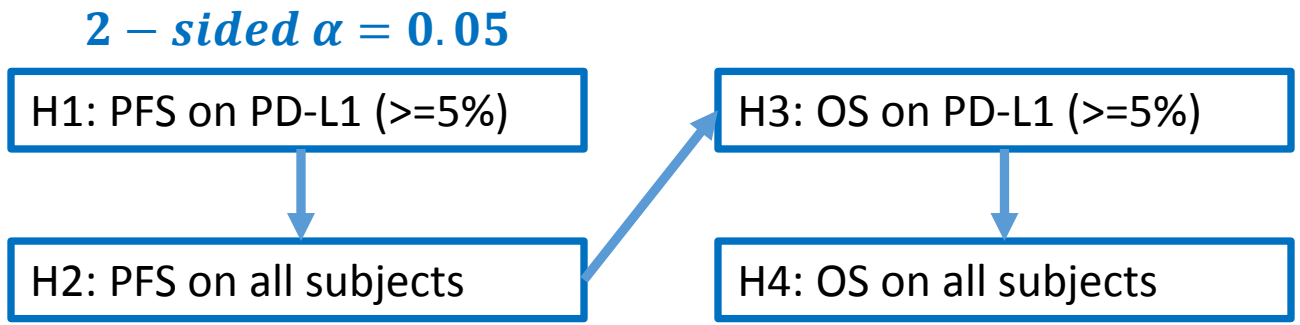
Motivation: Phase III, anti-PD-L1 Monotherapy Studies

- Tecentriq, IMvigor-211), May 2017
  - Open label, monotherapy Tecentriq vs. chemotherapies
  - They tested high PD-L1 population (IC2/3), followed by any level of PD-L1 (IC1/2/3), then overall population (ITT).
  - They failed at the primary endpoints (OS).



Motivation: Phase III, anti-PD-1 Monotherapy Studies

- Opdivo, Phase III on NSCLC (CheckMate-026), Aug 2016
  - Open label, monotherapy Opdivo vs. chemotherapies
  - Failed at primary endpoint (PFS) in subpopulation PD-L1 >= 5%



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Multiplicity Adjustment in Oncology Trials

Strongly Control Family-wise Type I error

- Label as driver: Dual-Primary, Primary/Secondary
  - Subpopulation – biomarker/genomic characteristics (e.g. PD-L1/PD-1)
  - Multiple Endpoints: OS, PFS, ORR, DCR, DOR etc.
  - Dose-ranging (high-dose/low-dose) etc.
- Interim analysis – Group Sequential Design

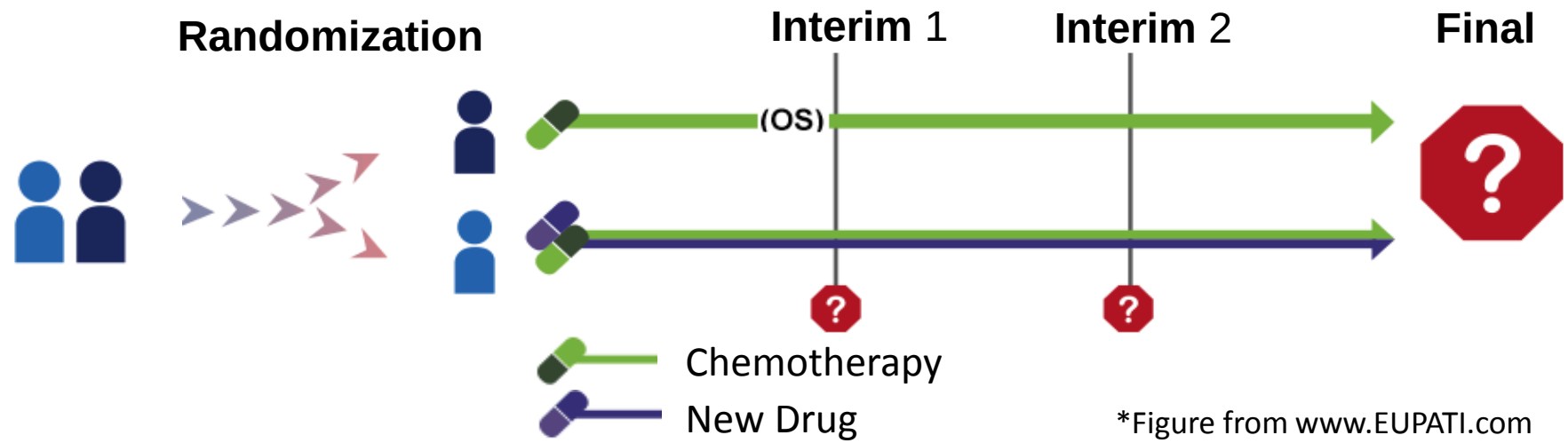

*Figure from www.EUPATI.com

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Interim analysis – Group Sequential Design

***Temporal correlations* in interim analyses and final analysis.**

- *Pocock (1977)* presented constant Type I error in interim analyses and final analysis $\alpha_2^*(t) = \alpha ln\{1 + (e-1)t\}$
- *O'Brien and Fleming (1979)* showed more conservative and unequal bounds in earlier stages $\alpha_1^* = 2\{1 - \Phi(z_{\alpha/2}/t^{1/2})\}$
- *Lan and DeMets (1983)* demonstrated a non-decreasing alpha-spending function and proposed (*Kim and DeMets, 1987*) the function with parameterϱ, $\alpha_3^*(\varrho, t) = \alpha t_k^{\varrho}$
- *Maurer and Bretz (2013)* published Graphical Approach in group sequential design when having multiple hypotheses

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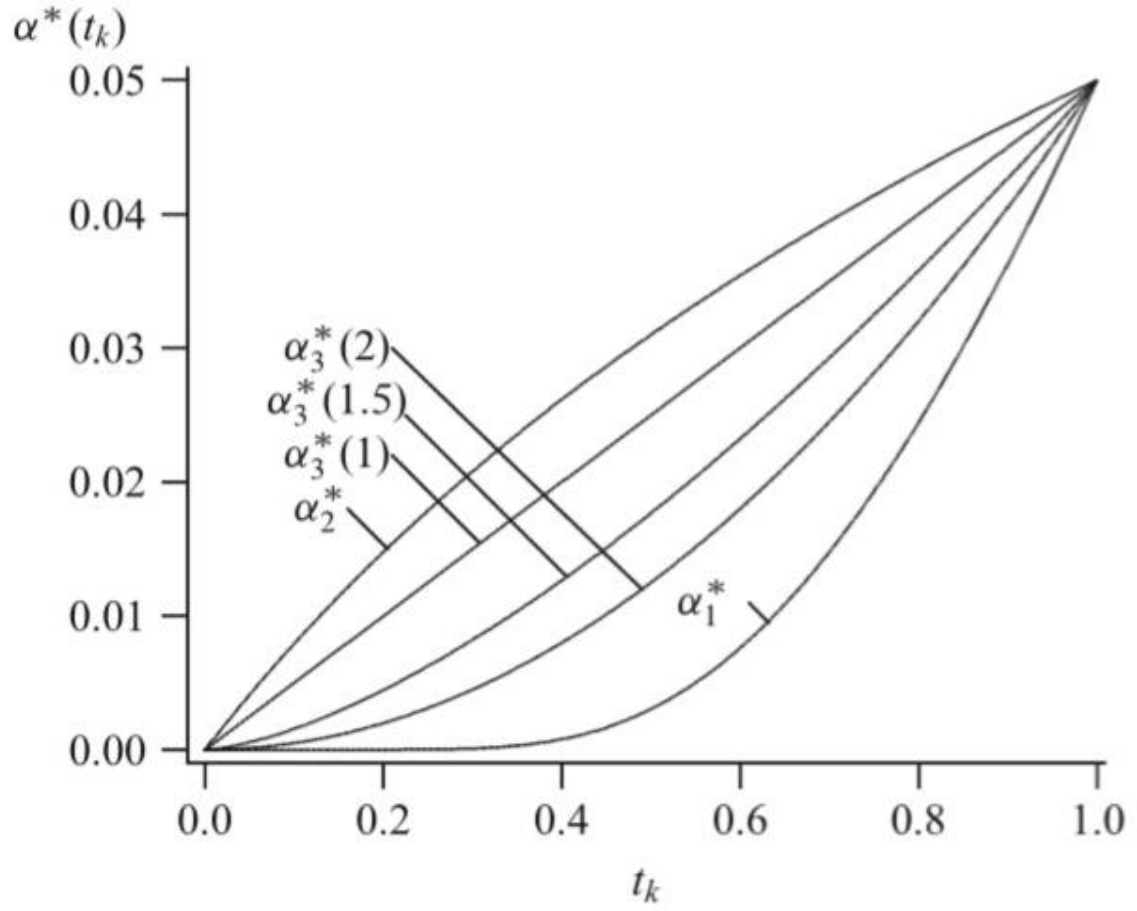
Interim analysis – Group Sequential Design



α_1^*: O'Brien and Fleming
α_2^*: Pocock
α_3^*: Kim and DeMets

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Sub-population: Population correlations in subgroups and overall population.

- *Chen and Beckman (2009)*: use prior information (Phase II) to construct optimal alpha-spending function to subgroup and overall population in Phase III trials.
- *Spiessens and Debois (2010)*: use Group sequential design method in subgroup analysis.
- Limited published research onboth temporal and population correlation.

Method Set Up: Complete Correlation Structure (CCS)

- Suppose a 2-arm trial comparing treatment effect in both a biomarker subgroup and overall population
- Information time: t_{ki}, $0 < t_{ki} \leq 1$
- Proportion of population (prevalence) p_{ki}, $0 < p_{ki} \leq 1$
- Stage: $k = 1, 2, \ldots, K$
- Population: $i = 1$ is subgroup, $i = 2$ is overall population
- $p_{k^*i} = n_{ki}/n_{KI}$
- n_{ki} is the number of observations at stage k in population i

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Method Set up: CCS (cont'd)

- Let Z_{ki} be the standardized test statistics and, under H_0, asymptotically follows a multivariate normal distribution
- $$Z_{ki} \sim N(\mathbf{0}, \boldsymbol{\Sigma}_{adj}) = N\left(\begin{pmatrix} 0 \\ \vdots \\ \vdots \\ 0 \end{pmatrix}, \begin{pmatrix} 1 & \sigma^2_{1,2} & \cdots & \sigma^2_{1,2k} \\ \sigma^2_{2,1} & 1 & \vdots & \vdots \\ \vdots & \vdots & 1 & \vdots \\ \sigma^2_{2k,1} & \cdots & \cdots & 1 \end{pmatrix} \right)$$
- $E(Z_{ki}) = \boldsymbol{\theta}\sqrt{\frac{n_{ki}}{4}}$ when H_a is true (e.g. 1:1 randomization ratio)
- $$COV(Z_{ki}, Z_{k'i'}) = \frac{\min(p_{ki}, p_{k'i'})\min(t_{ki}, t_{k'i'})}{\sqrt{p_{ki}t_{ki}p_{k'i'}t_{k'i'}}} = \sqrt{\frac{\min(p_{ki}, p_{k'i'})\min(t_{ki}, t_{k'i'})}{\max(p_{ki}, p_{k'i'})\max(t_{ki}, t_{k'i'})}}$$

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CCS: a simple example

- We have a 2-arm trail, only 1 interim analysis at 50% time is planned (k=2).
- The proportion of subgroup is 50%.
- So, t_{1i}=0.5, t_{2i}=1, p_{k1}=0.5, p_{k2}=1
- One-sided test, equally split FWER 0.025 to subgroup and overall population (0.0125 to each population)
- Correlation matrix $\boldsymbol{\Sigma}_{adj}$ for interim analysis Z_{11}, Z_{12} and final analysis Z_{21}, Z_{22} will be

$$\begin{bmatrix} 1 & \sqrt{0.5} & \sqrt{0.5} & 0.5 \\ \sqrt{0.5} & 1 & 0.5 & \sqrt{0.5} \\ \sqrt{0.5} & 0.5 & 1 & \sqrt{0.5} \\ 0.5 & \sqrt{0.5} & \sqrt{0.5} & 1 \end{bmatrix}$$

Evaluation of CCS

- Adjusted Type I error
  - $P_{H_0}\left(Z_{11} > b_1' \; or \; Z_{12} > b_1' \; or \; Z_{21} > b_2' \; or \; Z_{22} > b_2' | \boldsymbol{\Sigma}_{adj}\right) - FWER = 0$
- Adjusted population power
  - $P_{H_a}\left(Z_{11} > b_1' \; or \; Z_{21} > b_2' | \Sigma_{adj}\right)$ and $P_{H_a}\left(Z_{12} > b_1' \; or \; Z_{22} > b_2' | \boldsymbol{\Sigma}_{adj}\right)$
- Adjusted event(sample) size
  - $SS_{sub} = GS(\alpha_{sub}') \; and \; SS_{ova} = GS(\alpha_{ova}')$

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Evaluation of CCS

Improvements of CCS		
	Original Design	**CCS-adjusted Design**
Type I error	0.0125	0.0147
Power	0.92	0.9
Event size	570/1140	551/1102

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Evaluation of CCS

- Type I error

Figure 1. Adjusted Type I Error (α'_{sub}) vs. Proportion of Subgroup (p_{k1})

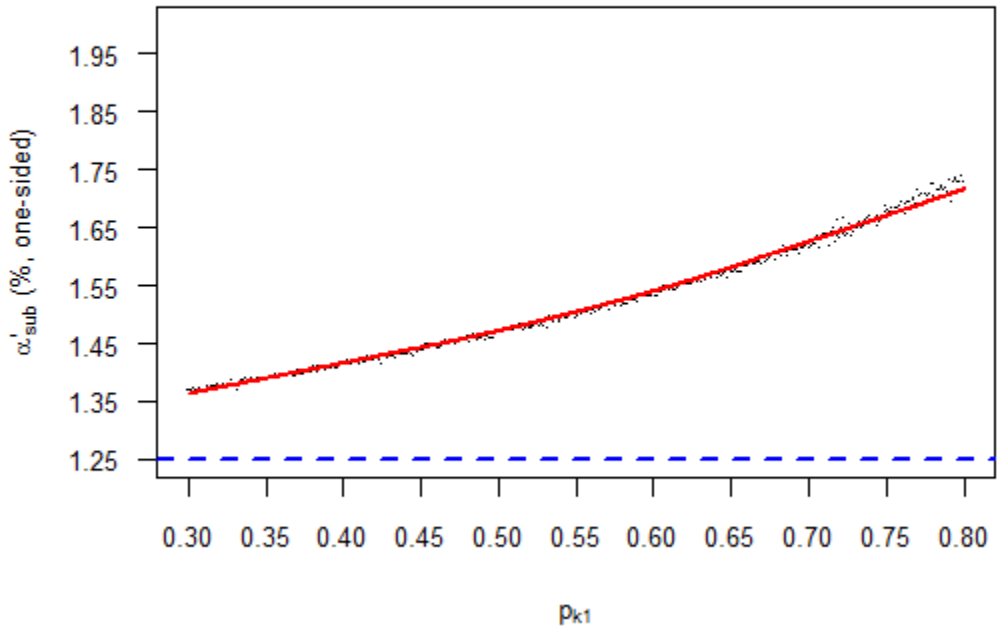
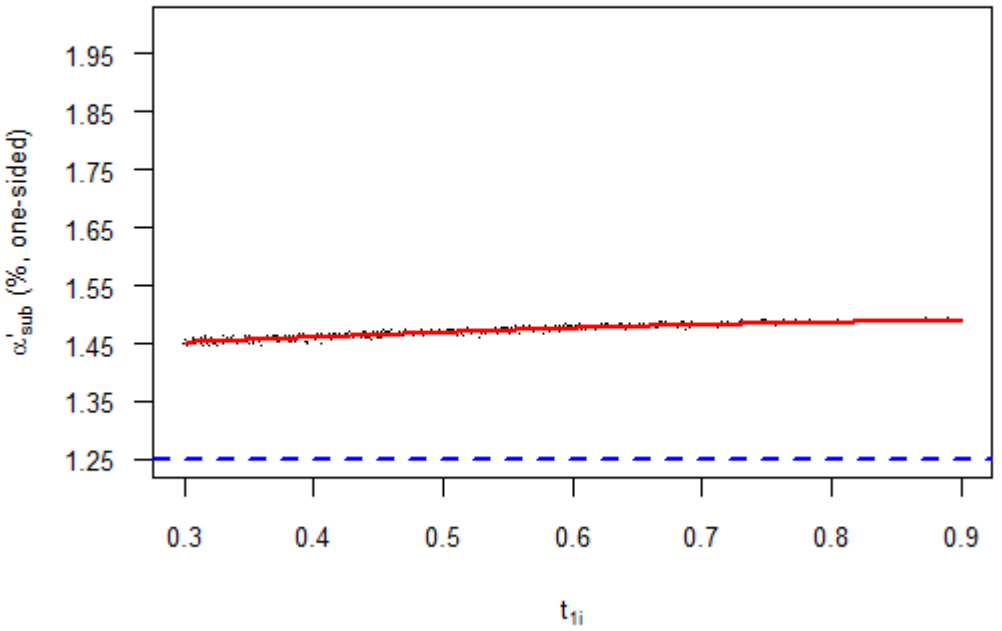


Figure 4. Adjusted Type I Error (α'_{sub}) vs. IA Proportion (t_{1i})



Evaluation of CCS

- Power

Figure 2. Adjusted Population-based Power vs. Proportion of Subgroup (p_{k1})

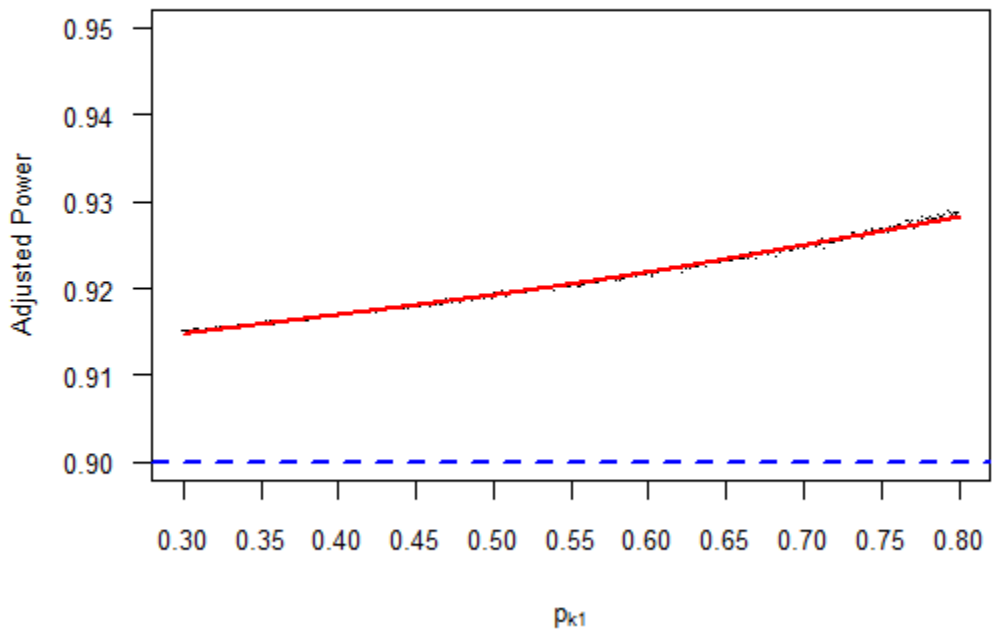
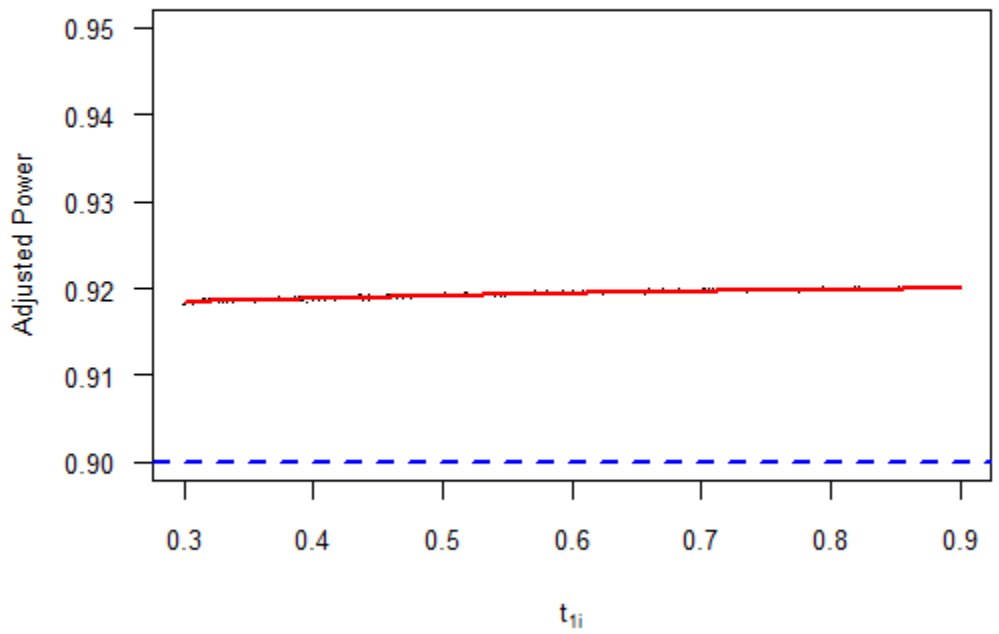


Figure 5. Adjusted Population-based Power vs. IA Proportion (t_{1i})



Evaluation of CCS

- Event Size

Figure 3. Sample Size Saved (%) vs. Proportion of Subgroup (p_{k1})

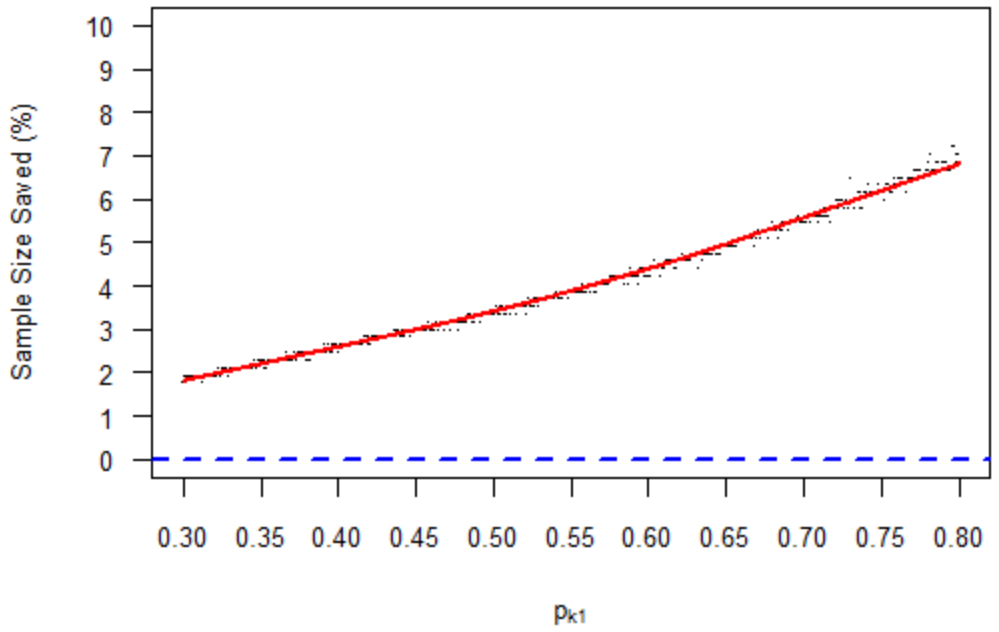
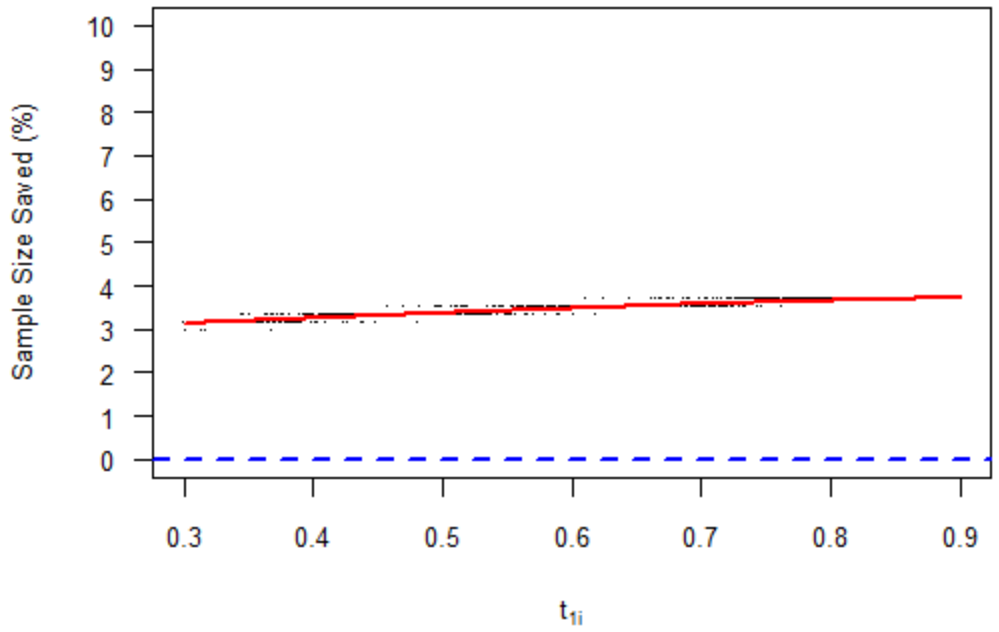
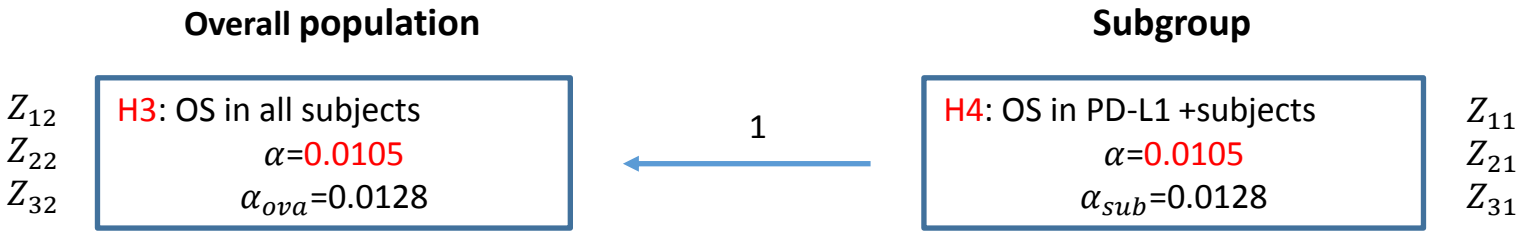


Figure 6. Sample Size Saved (%) vs. IA Proportion (t_{1i})



Discussion: Extended Application of CCS

- CCS in group sequential design can be applied to normal, binary, survival type of outcomes.
  - The advantage of standardized test statistics.
- CCS can be applied to most group sequential methods
  - Pocock, O'Brien and Fleming, Lan and DeMets, Kim and Demets, Maurer and Bretz.
- Graphical approach:
  - Only original Bonferroni-Holm amount of α (in red) in graphical approach can be transferred to the next hypothesis.



Extended Application of CCS

- CCS can be applied to multiple-arm trials.
  - EX. A 3-arm trial comparing treatment effect in High-dose vs. placebo and low-dose vs. placebo.
  - The covariance matrix will be extended to a 8*8 matrix
  - Off-diagonal sub-matrix is the correlations of test statistics from high-dose group and low-dose group

$$\begin{bmatrix} M1_{4\times4} & M2_{4\times4} \\ M3_{4\times4} & M4_{4\times4} \end{bmatrix}$$

$$COV(Z_{Hki}, Z_{Lk'i'}) = \frac{\min(p_{Hki}, p_{Lk'i'})\min(t_{Hki}, t_{Lk'i'})}{\sqrt{p_{Hki}t_{Hki}p_{Lk'i'}t_{Lk'i'}}} = \sqrt{\frac{\min(p_{Hki}, p_{Lk'i'})\min(t_{Hki}, t_{Lk'i'})}{\max(p_{Hki}, p_{Lk'i'})\max(t_{Hki}, t_{Lk'i'})}}$$

  - The correlation is contributed from placebo observations

Conclusion

- Complete Correlation Structure (CCS) accounts for *temporal* correlations and *population* correlations in test statistics.
- CCS will increase nominal Type I error and power, and require less sample size.
- Proportion of subgroup dominates the impact of CCS.
- CCS can be valuable in cost saving or hidden benefits in the pocket.
- Easy and comprehensive application to existing methods and current clinical trial designs.

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