A simulation study to compare Group Sequential Designs for Subpopulation testing and Enrichment

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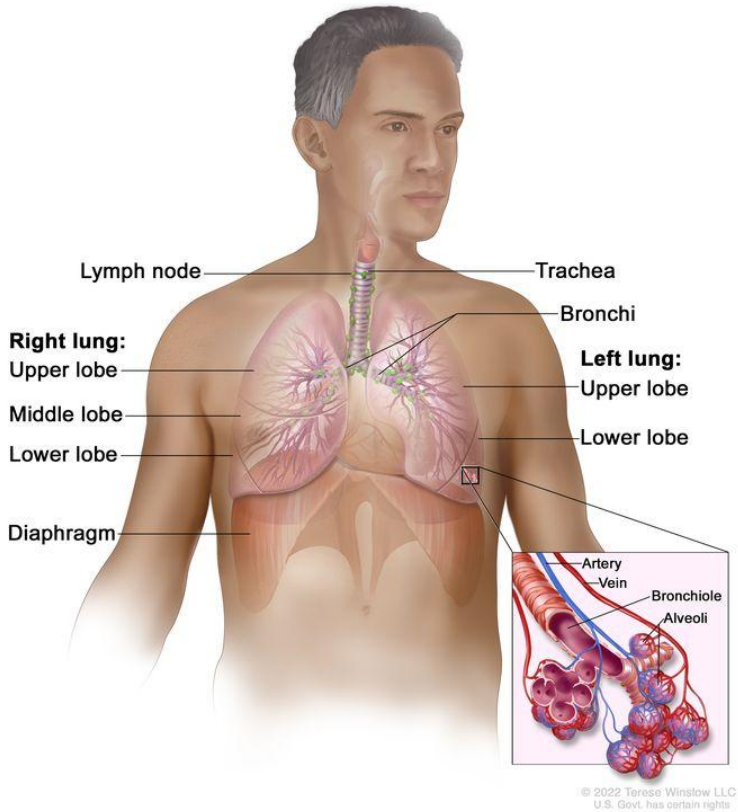
Background

- Non-Small Cell Lung Cancer (NSCLC) is the most common type of lung cancer (~85% of cases)
- Unmet need: Despite current therapies, many patients relapse, and treatment response is inconsistent
- Introducing a new peri-operative treatment
- Opportunity to have big impact on the disease
- Opportunity to increase cure rates with a peri-operative approach
  - → Still high unmet need – only ~20% pCR (pathological complete response) rates observed
  - → High rates of recurrence for patients who do not achieve pCR
- Biological heterogeneity in response to experimental treatment suggests that level of biomarker expression may predict better treatment outcomes
- Large commercial opportunity
- Competitive landscape



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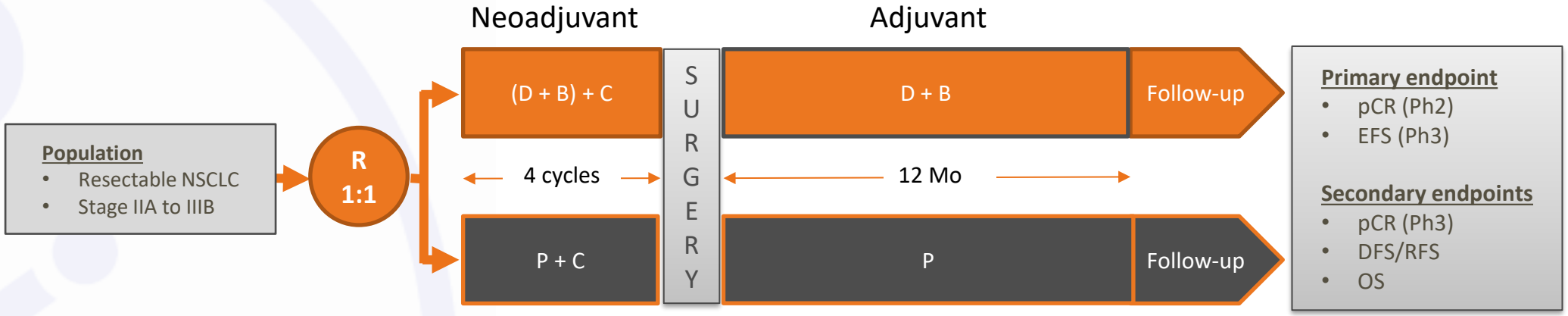
A randomized, open-label phase 2/3 peri-operative trial of Drug D + B in combination with chemotherapy C in resectable NSCLC

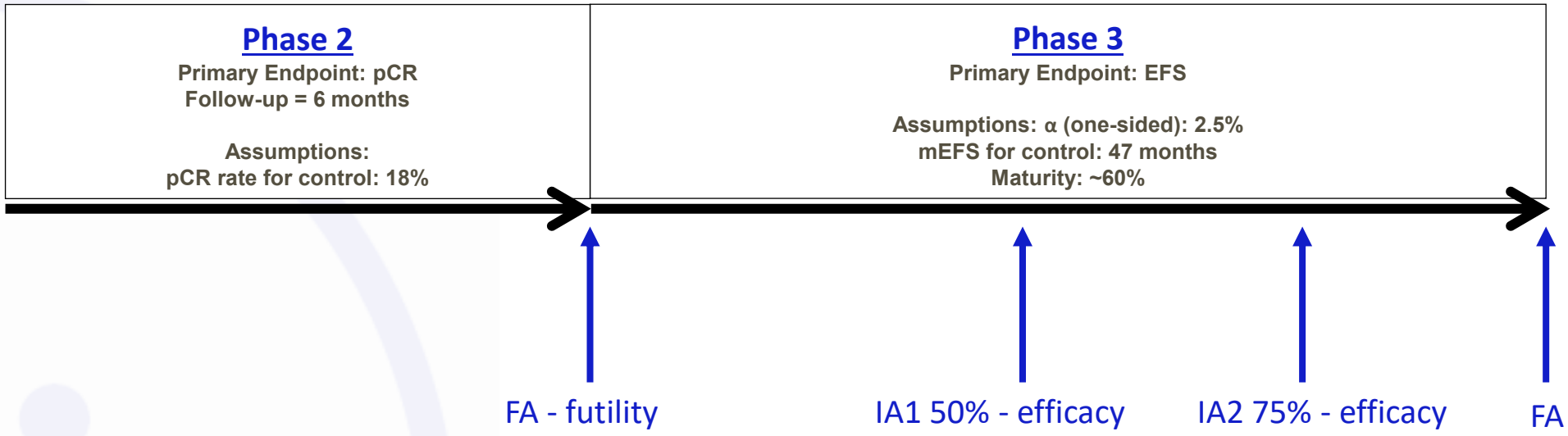


Subgroups:
- (S^-) Biomarker < x [prevalence 40%]
- (S^+) Biomarker ≥ x [prevalence 60%]

All comers: FP = S^- + S^+

- Study design: Phase 2/3, peri-operative treatment in resectable NSCLC
- Patient population: Stage IIA–IIIB, resectable NSCLC
- Two treatment arms: D + B (+ chemotherapy) vs. P (+ chemotherapy)
- Endpoints:
  - Phase 2: Pathological Complete Response (pCR) - defined as the absence of viable tumor cells in resected tissue
  - Phase 3: Event-Free Survival (EFS) - time to recurrence, progression, or death

Which strategy when potential subgroup effect?



- Group sequential design in Phase 3 with 2 IAs for efficacy
- Potential identified subgroup more likely to respond to treatment with uncertainty on possible effect on the whole population or subgroup only
- Claim on both population (FP and S^+) would be appreciated
- Stop trial when whole population significant
- Which strategy?

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Outline

1. Introduction
2. Methods
    1. Phase 2/3 GSD with population only
    2. Fallback design Phase 2/3 with subpopulations testing
        - Hierarchical procedure
        - Bonferroni
        - Holm / Ye (2013)
        - Zhao et al. (2010) with and without enrichment
    3. Enrichment Phase 2/3
        - “Largest population from the first effective subgroup”
    4. Fallback design and Enrichment Phase 2/3 with subpopulations testing
3. Simulations
4. Conclusion

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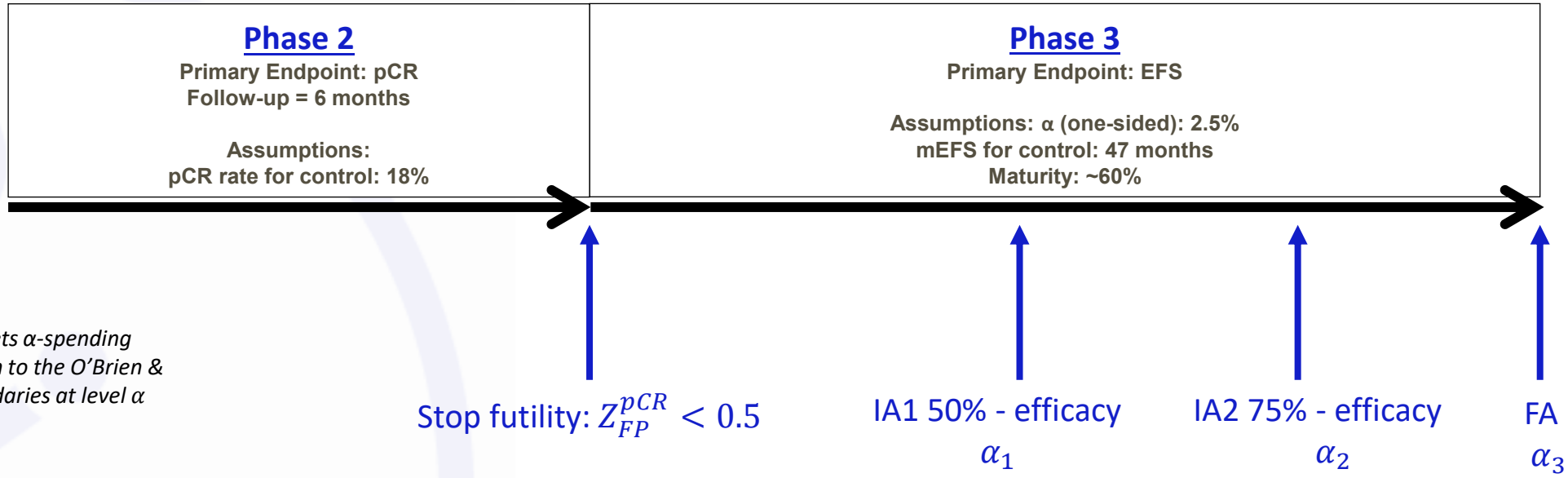
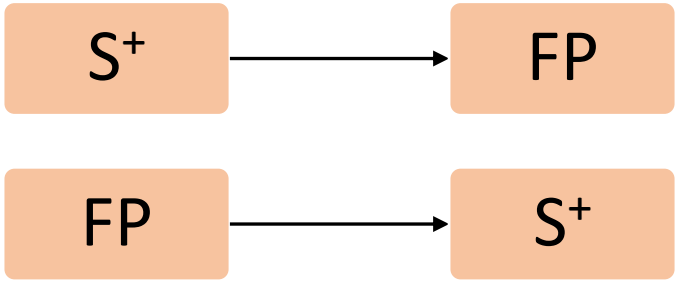
Simple procedures



1. GSD with full population (no subgroup considered) as a reference for comparison: test FP only
2. Hierarchical: test S^+ → test FP
3. Hierarchical: test FP → test S^+



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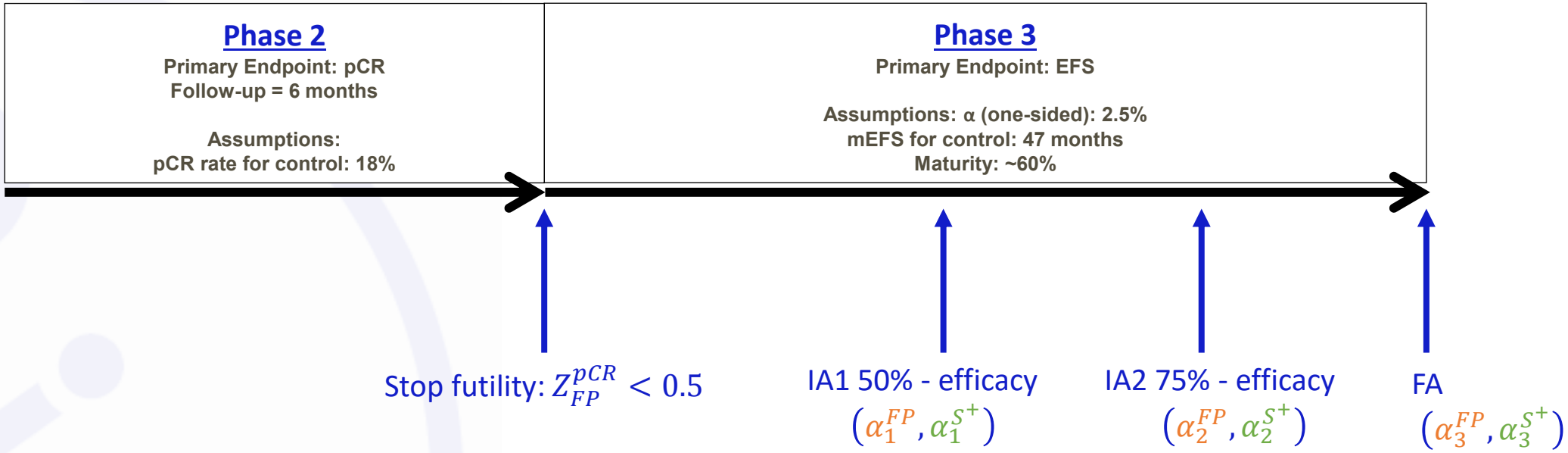
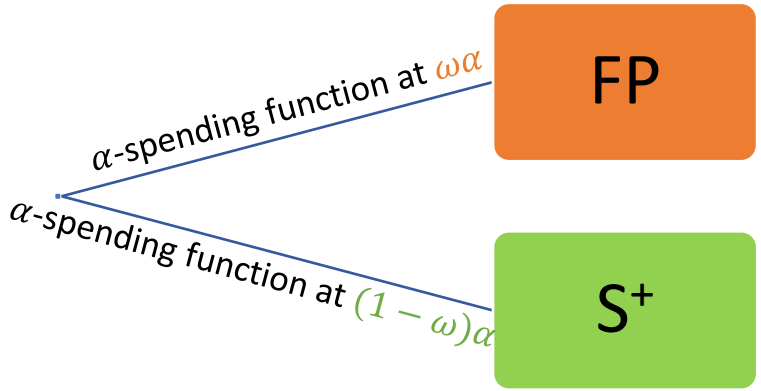
Bonferroni & Holm procedure (Ye et al. Stat Med 2013)



4. Bonferroni: test both FP and S⁺



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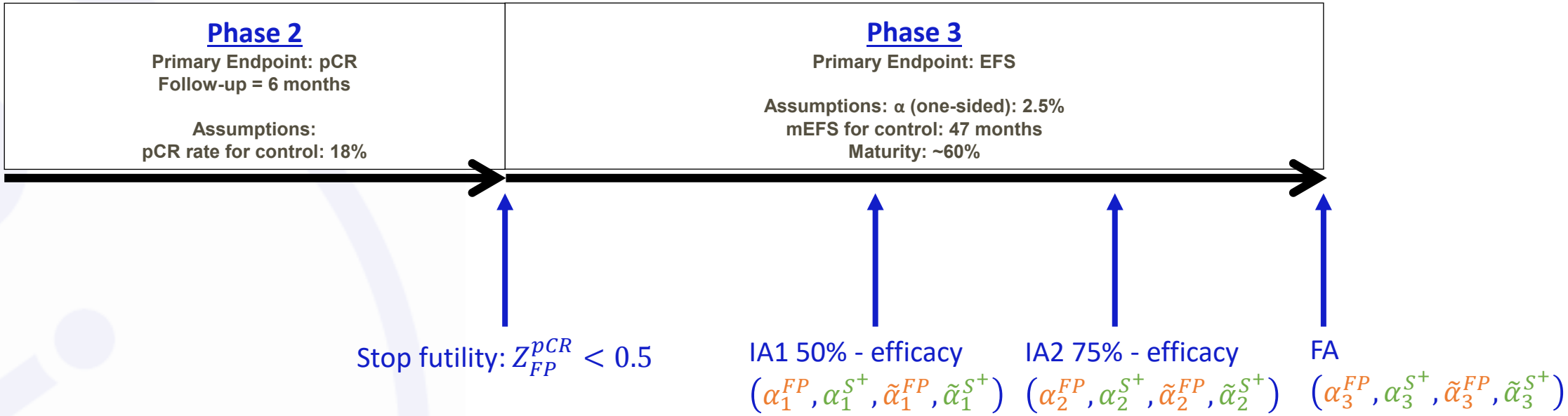
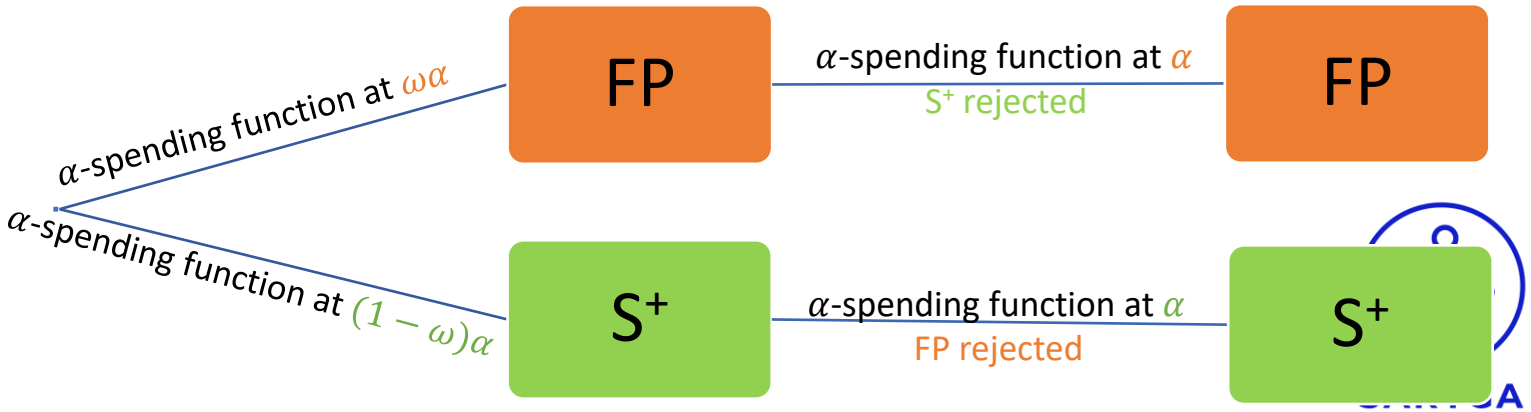
Bonferroni & Holm procedure (Ye et al. Stat Med 2013)

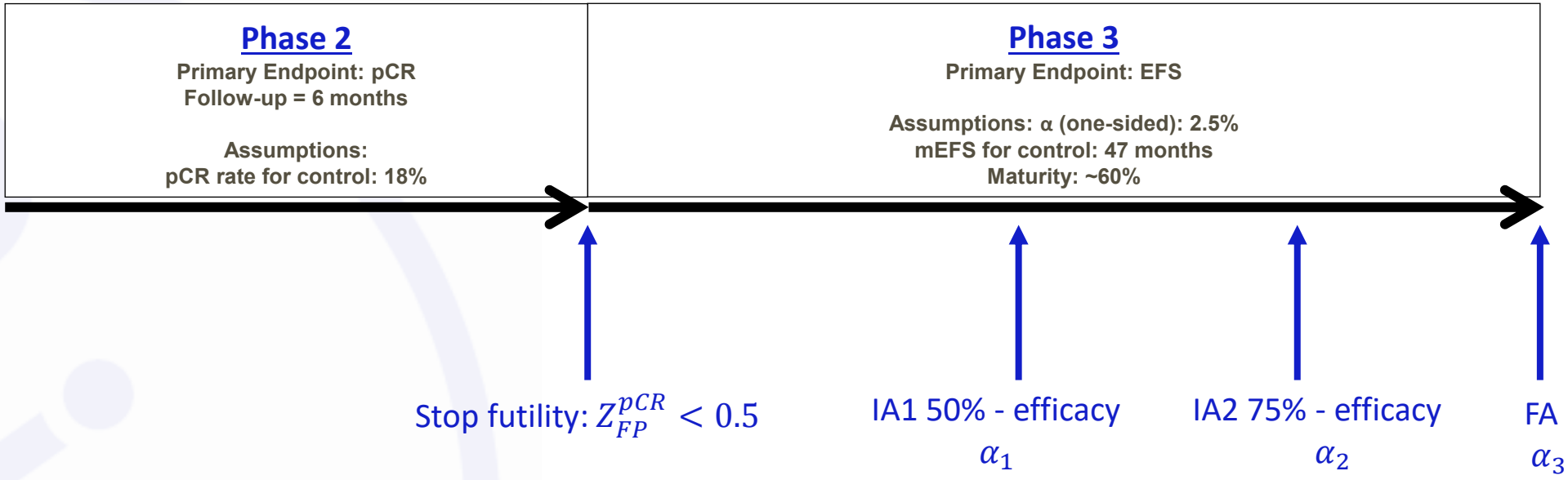


4. Bonferroni: test both FP and S⁺
5. Holm: test both FP and S⁺



Ye Y, Li A, Liu L, Yao B. A group sequential Holm procedure with multiple primary endpoints. *Stat Med*. 2013;32(7):1112-1124

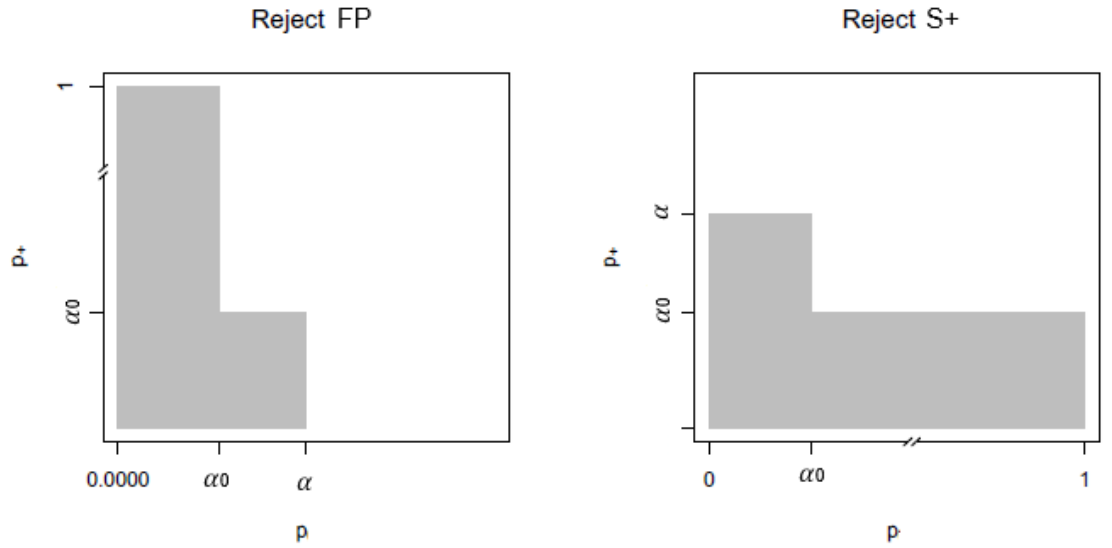
Zhao procedure (Zhao et al. Stat. Biopharm. Res. 2010)



6. Zhao: test both FP and S+

α_0 to have a trade-off between FP and S+

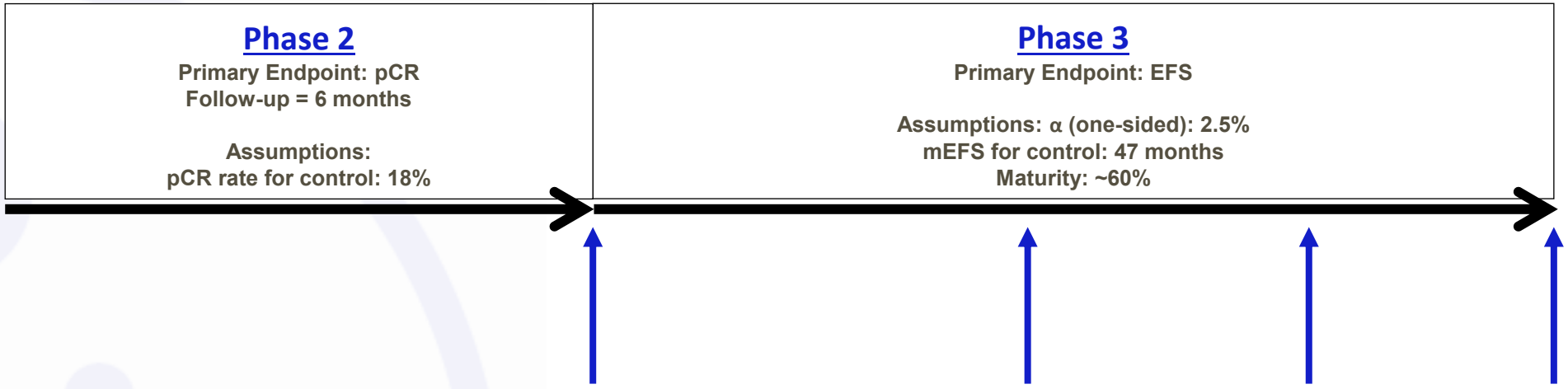
- If α_0 close to α: favor FP
- If α_0 close to 0: favor S+



➔ without enrichment

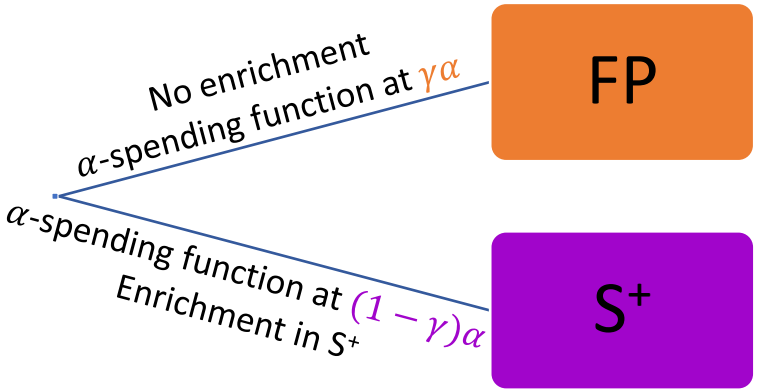
➔ with enrichment: increase prevalence of the sensitive subgroup in the study compared to prevalence in the general population

Enrichment



Enrich: continue in FP if S⁻ satisfy $Z_{S^-}^{pCR} \geq z_e$,
OR in S⁺ only if $Z_{S^-}^{pCR} < z_e$ and $Z_{S^+}^{pCR} \geq z_e$

7. Enrichment: select and test either FP or S⁺



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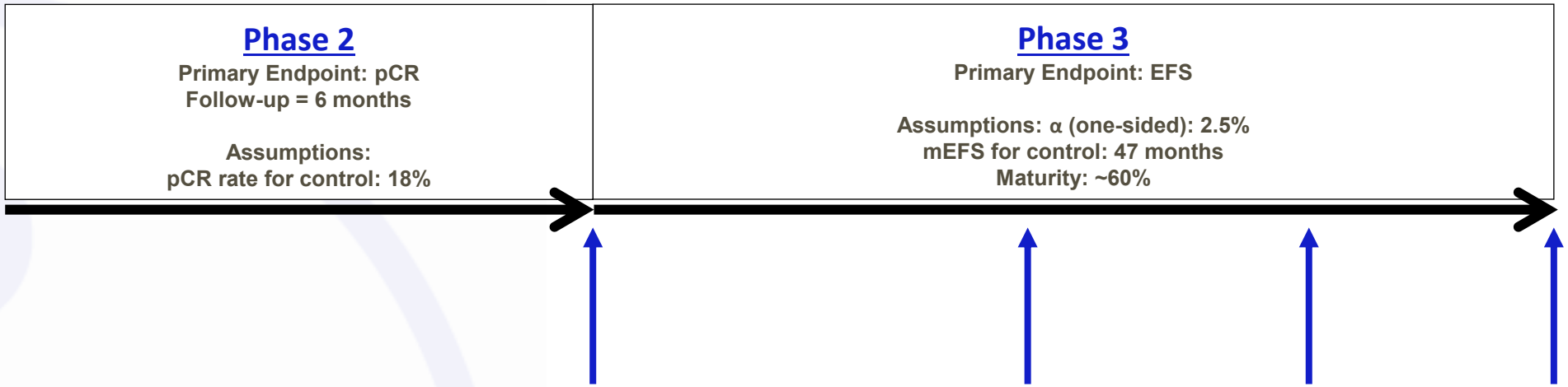
Enrichment + Holm procedure



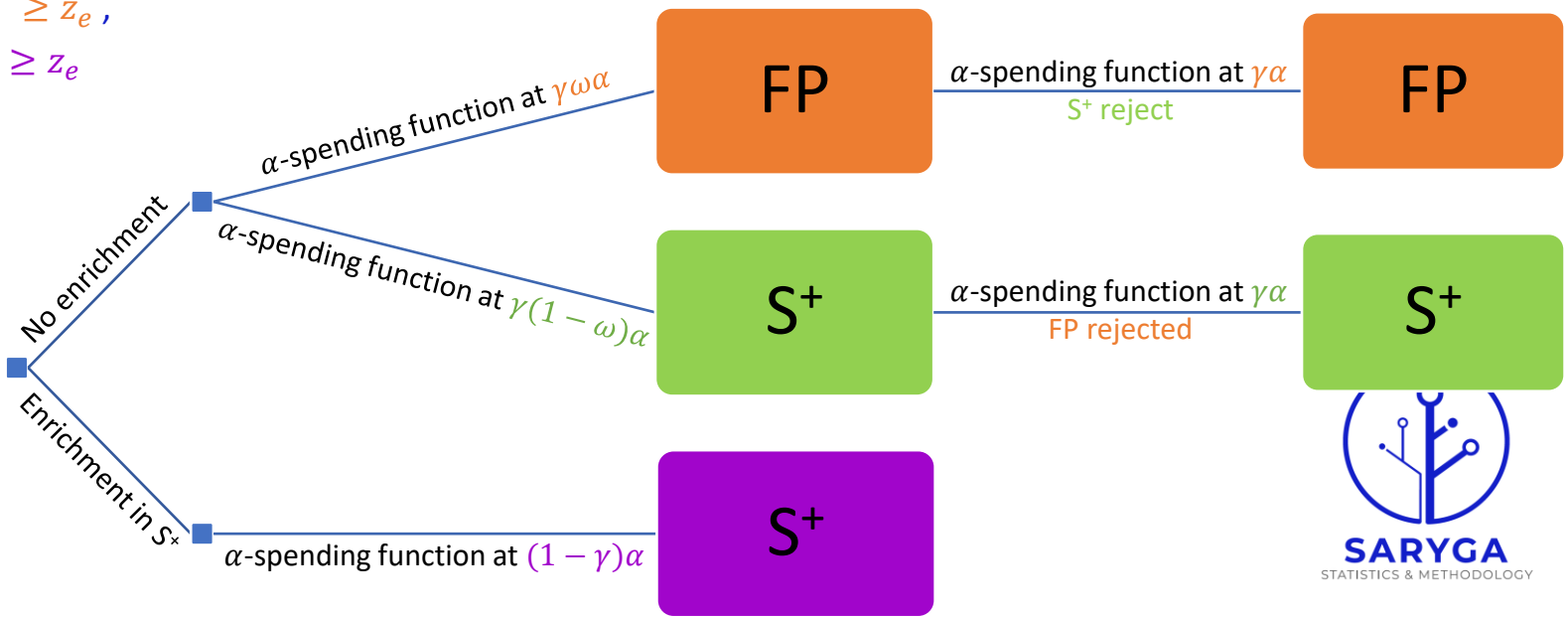
Stop futility: $Z_{S^-}^{pCR} < 0.5$ and $Z_{S^+}^{pCR} < 0.5$

IA1 50% - efficacy $\left(\alpha_1^{FP}, \alpha_1^{S^+}, \alpha_1^{S}, \tilde{\alpha}_1^{FP}, \tilde{\alpha}_1^{S^+}\right)$

IA2 75% - efficacy $\left(\alpha_2^{FP}, \alpha_2^{S^+}, \alpha_2^{S}, \tilde{\alpha}_2^{FP}, \tilde{\alpha}_2^{S^+}\right)$

FA $\left(\alpha_3^{FP}, \alpha_3^{S^+}, \alpha_3^{S}, \tilde{\alpha}_3^{FP}, \tilde{\alpha}_3^{S^+}\right)$

Enrich: continue in FP if S⁻ satisfy $Z_{S^-}^{pCR} \geq z_e$,
or in S⁺ only if $Z_{S^-}^{pCR} < z_e$ and $Z_{S^+}^{pCR} \geq z_e$



8. Enrichment + Holm:
   - Select and test S+
   - Or select FP and test both FP and S+

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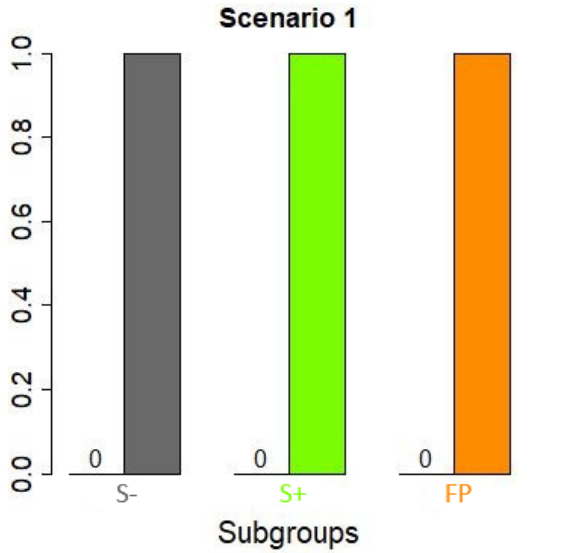
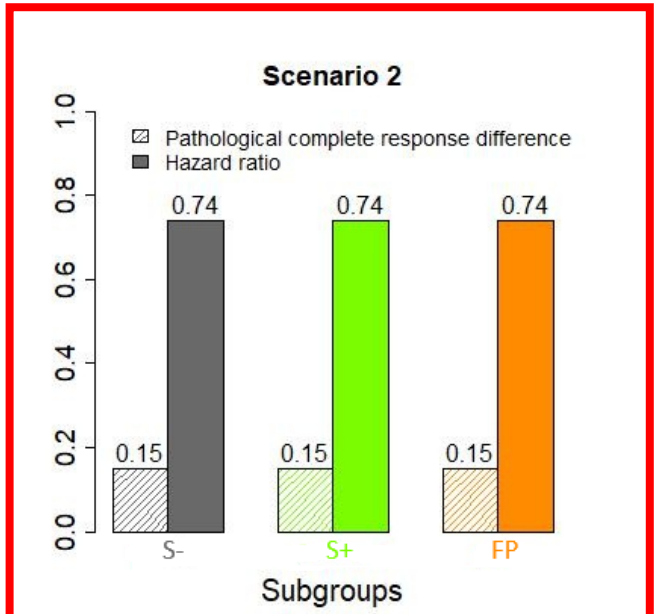
Simulations

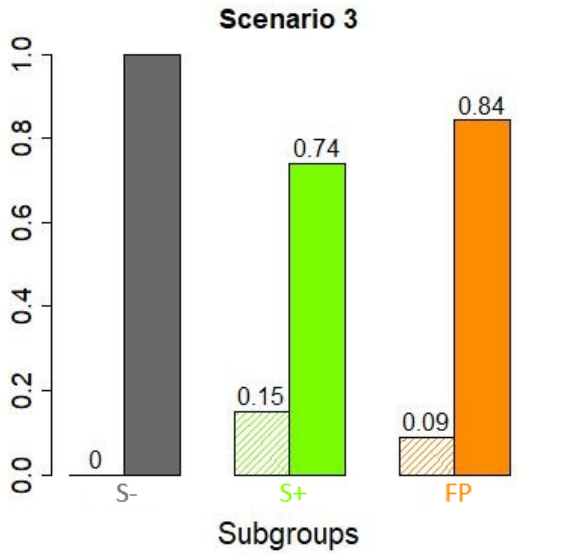
- N = 820 patients included in total
  (including patients in S^- when enrichment)

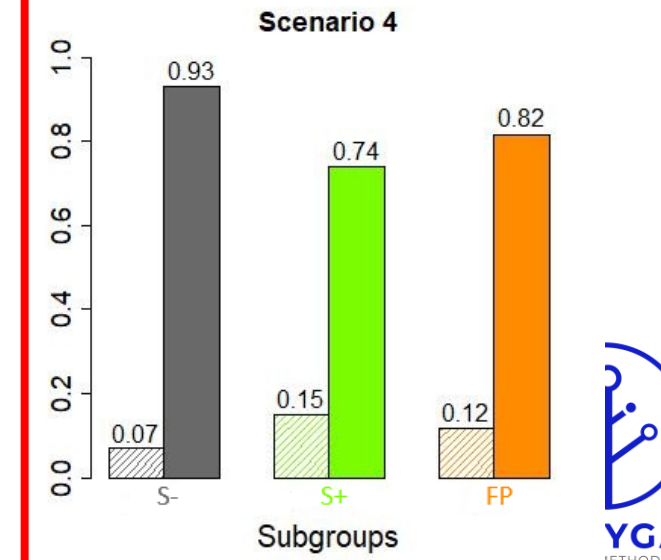
Phase 2	Phase 3
Primary Endpoint: pCR Follow-up = 6 months Assumptions: pCR rate for control: 18%	Primary Endpoint: EFS Assumptions: α (one-sided): 2.5% mEFS for control: 47 months Maturity: ~60%

- IAs at 50% and 75% IF
- Prevalences (S^-, S^+) = (40%, 60%)
- Number of patients for phase 2:
  260 patients (130 par arm)

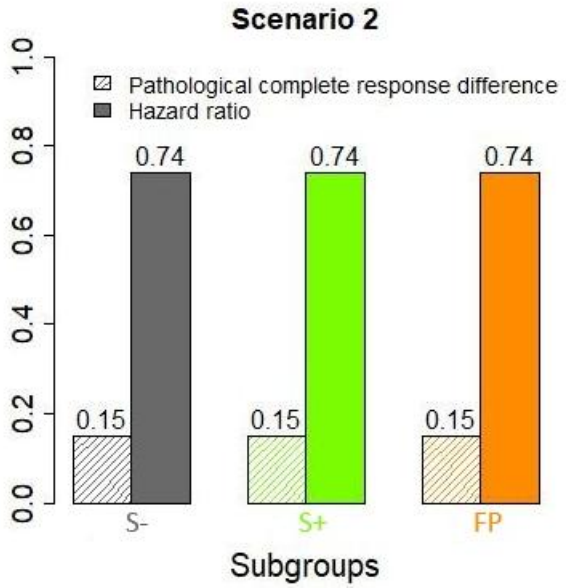








Scenario 2



- Sample size calculated to have 90% power for a simple seamless Phase 2/3 without considering subpopulations when there is an effect in all groups

		Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
Scenario	Design	Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
Sc2	Full pop	1%	19	.	27%	50	70%	71	90%	101	90%	.

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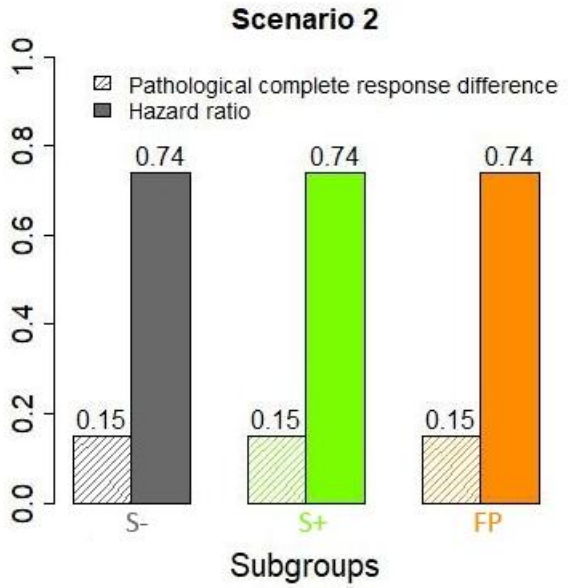
Scenario 2



- Hierarchical S^+->FP:
  - Power around 70% for both: when S^+ is significant, FP is also usually significant as more sample size/power
  - Trials stop at later analysis

		Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
Scenario	Design	Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
Sc2	Full pop	1%	19	.	27%	50	70%	71	90%	101	90%	.
	Fallback Hierarchical S->FP	1%	19	.	10%/12%	50	42%/45%	71	70%/72%	101	72%	70%
	Fallback Hierarchical FP->S	1%	19	.	26%/10%	50	70%/32%	71	90%/42%	101	90%	42%

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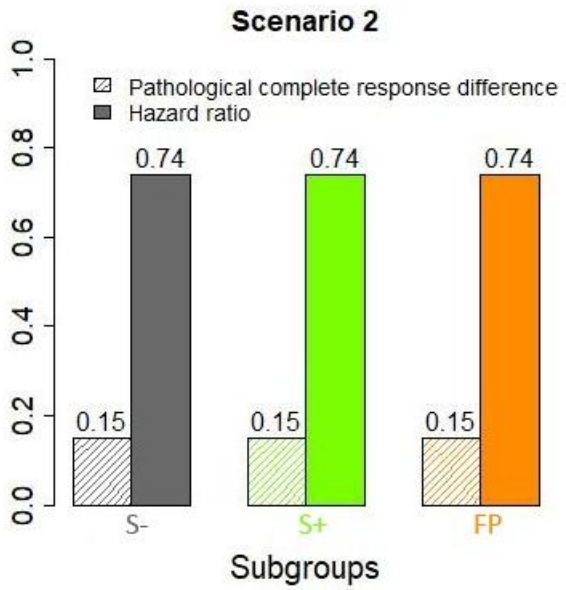
Scenario 2

- Hierarchical FP->S:
  - 90% power for FP as expected
  - Low power (42%) for S^+ as:
    - Trial not powered for S^+/would require higher sample size (↘-18%)
    - Trial stop when FP significant so potentially at previous IAs with even lower sample size/power (↘-30%)



		Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
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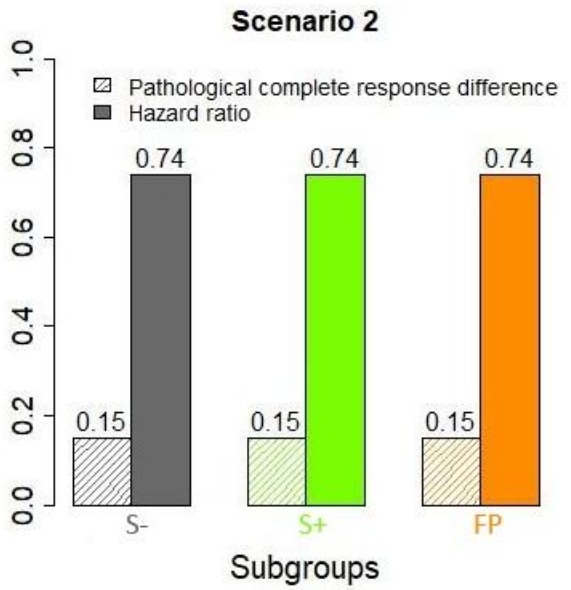
Scenario 2



- Bonferroni & Holm:
  - High power for FP: 85%/86%, only a small decrease of power
  - But more chance to stop at later stages
  - 60%/70% chances to reject also S^+, with Holm > Bonferroni as expected

		Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
Scenario	Design	Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
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	Fallback Hierarchical FP->S	1%	19	.	26%/10%	50	70%/32%	71	90%/42%	101	90%	42%
	Fallback Bonferroni	1%	19	.	16%/6%	50	58%/33%	71	85%/62%	101	86%	60%
	Fallback Holm	1%	19	.	17%/9%	50	60%/42%	71	86%/70%	101	86%	70%

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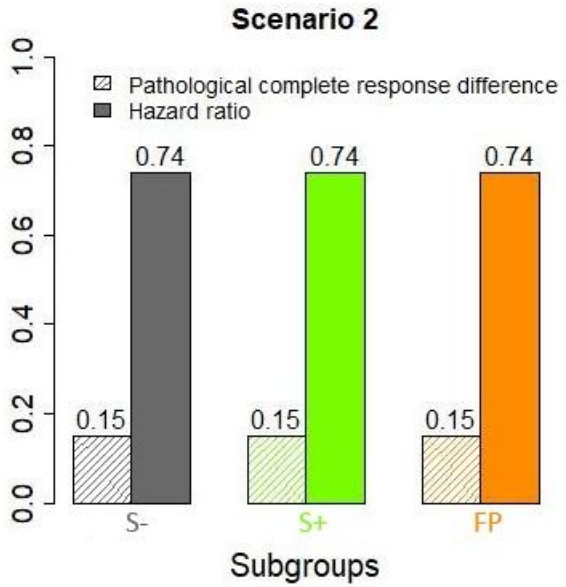
Scenario 2



- Zhao:
  - With $\alpha_0 = \frac{\alpha}{5}, \frac{\alpha}{2}, \frac{4\alpha}{5}$ corresponding to different compromise between FP and S⁺
  - 81%/89% power for FP depending on α_0 and 45%/58% for S⁺

		Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
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	Fallback Holm	1%	19	.	17%/9%	50	60%/42%	71	86%/70%	101	86%	70%
	Fallback Zhao (0.6,0.4) a0=a/5	1%	19	.	16%/12%	50	55%/40%	71	81%/58%	101	82%	57%
	Fallback Zhao (0.6,0.4) a0=a/2	1%	19	.	21%/11%	50	62%/36%	71	86%/50%	101	87%	49%
	Fallback Zhao (0.6,0.4) a0=4a/5	1%	19	.	25%/11%	50	67%/33%	71	89%/45%	101	89%	44%

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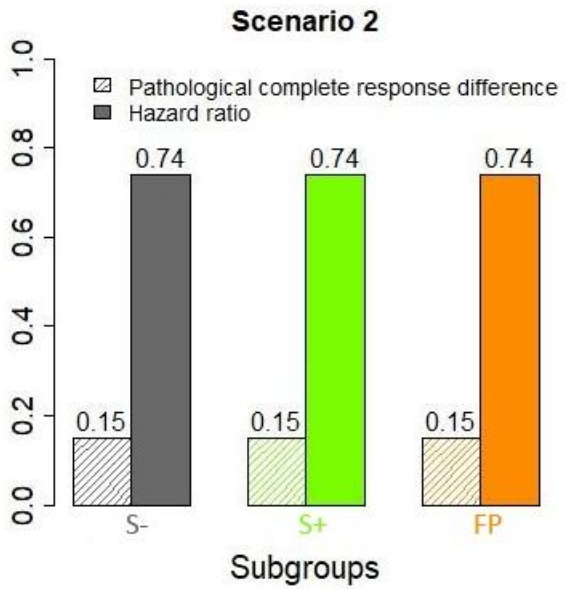
Scenario 2



- Zhao with enrichment:
  - For the same $\alpha_0 = \frac{\alpha_k}{2}$, it slightly decreases power for FP, but increases power for S⁺
  - Timelines are slightly increased

Scenario	Design	Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
		Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
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	Fallback Zhao (0.6,0.4) a0=a/2	1%	19	.	21%/11%	50	62%/36%	71	86%/50%	101	87%	49%
	Fallback Zhao (0.6,0.4) a0=4a/5	1%	19	.	25%/11%	50	67%/33%	71	89%/45%	101	89%	44%
	Fallback Zhao with enrichment (0.75,0.25) a0=a/2	1%	19	.	18%/15%	53	58%/46%	73	84%/64%	103	88%	60%

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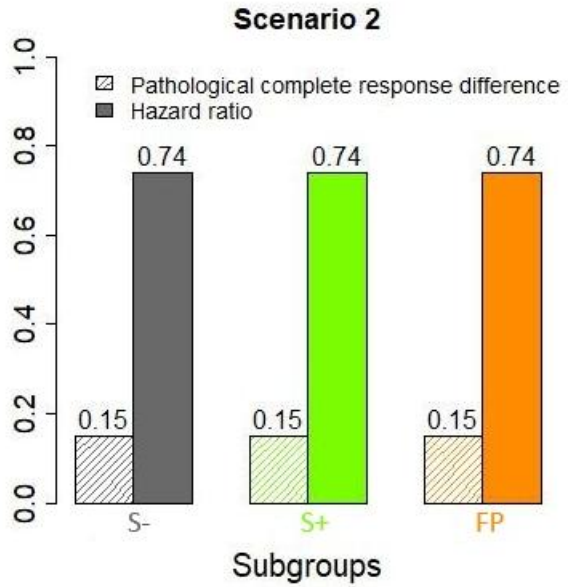
Scenario 2

- Enrichment:
  - Futility calibrated to have the same % of stopping under null scenario 1
  - With an α split in favor of FP and low chances to enrich: 93% chances to go with FP and 83% power for FP
  - Otherwise, highly decreases performance for FP as expected
  - By construction, no chance to reject S^+ if FP selected (thus only 3%-16%)
  - Enrichment may increase timelines by 10 months
  - 104 patients in non-responsive subgroup "lost" for final analysis when S^+ selected



Scenario	Design	Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
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	Fallback Zhao (0.6,0.4) a0=4a/5	1%	19	.	25%/11%	50	67%/33%	71	89%/45%	101	89%	44%
	Fallback Zhao with enrichment (0.75,0.25) a0=a/2	1%	19	.	18%/15%	53	58%/46%	73	84%/64%	103	88%	60%
	Enrichment (4/5,1/5) Zenrich=0	3%	19	93%/4%	22%/0%	50/61	62%/2%	71/81	83%/3%	101/111	86%	.
	Enrichment (4/5,1/5) Zenrich=1	3%	19	78%/20%	18%/1%	50/61	52%/7%	71/81	70%/14%	101/111	83%	.
	Enrichment (1/3,2/3) Zenrich=0	3%	19	93%/4%	11%/1%	50/61	49%/2%	71/81	77%/4%	101/111	80%	.
	Enrichment (1/3,2/3) Zenrich=1	3%	19	78%/20%	9%/3%	50/61	41%/11%	71/81	64%/16%	101/111	80%	.

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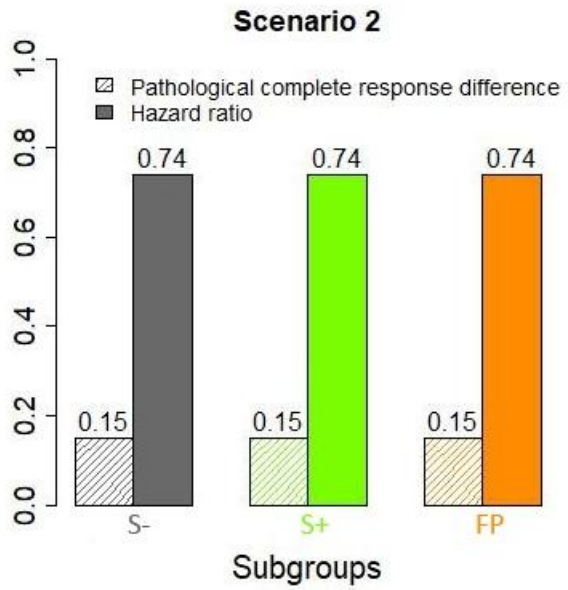
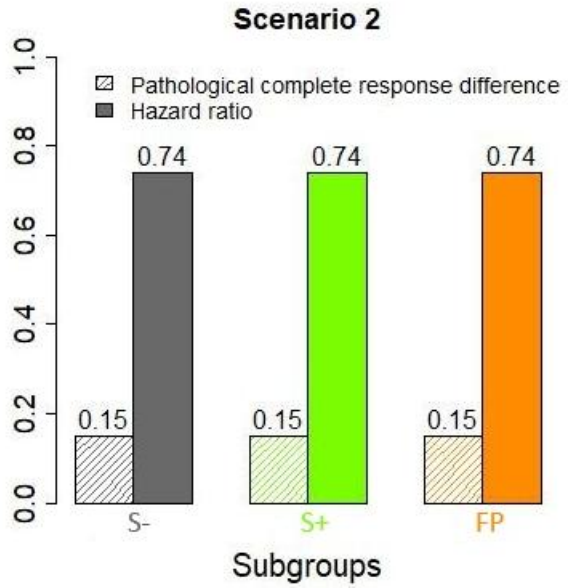
Scenario 2



- Enrichment+Holm:
  - Similar conclusion as for enrichment for rejection of FP and timelines
  - Compared to enrichment only, good chances to also reject S^+ (64%-67%)

Scenario	Design	Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
		Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
Sc2	Full pop	1%	19	.	27%	50	70%	71	90%	101	90%	.
	Fallback Hierarchical S->FP	1%	19	.	10%/12%	50	42%/45%	71	70%/72%	101	72%	70%
	Fallback Hierarchical FP->S	1%	19	.	26%/10%	50	70%/32%	71	90%/42%	101	90%	42%
	Fallback Bonferroni	1%	19	.	16%/6%	50	58%/33%	71	85%/62%	101	86%	60%
	Fallback Holm	1%	19	.	17%/9%	50	60%/42%	71	86%/70%	101	86%	70%
	Fallback Zhao (0.6,0.4) a0=a/5	1%	19	.	16%/12%	50	55%/40%	71	81%/58%	101	82%	57%
	Fallback Zhao (0.6,0.4) a0=a/2	1%	19	.	21%/11%	50	62%/36%	71	86%/50%	101	87%	49%
	Fallback Zhao (0.6,0.4) a0=4a/5	1%	19	.	25%/11%	50	67%/33%	71	89%/45%	101	89%	44%
	Fallback Zhao with enrichment (0.75,0.25) a0=a/2	1%	19	.	18%/15%	53	58%/46%	73	84%/64%	103	88%	60%
	Enrichment (4/5,1/5) Zenrich=0	3%	19	93%/4%	22%/0%	50/61	62%/2%	71/81	83%/3%	101/111	86%	.
	Enrichment (4/5,1/5) Zenrich=1	3%	19	78%/20%	18%/1%	50/61	52%/7%	71/81	70%/14%	101/111	83%	.
	Enrichment (1/3,2/3) Zenrich=0	3%	19	93%/4%	11%/1%	50/61	49%/2%	71/81	77%/4%	101/111	80%	.
	Enrichment (1/3,2/3) Zenrich=1	3%	19	78%/20%	9%/3%	50/61	41%/11%	71/81	64%/16%	101/111	80%	.
	Fallback Holm + Enrichment (4/5,1/10,1/10) Zenrich=0	3%	19	94%/4%	22%/8%	50/61	63%/39%	71/81	84%/67%	101/111	86%	65%
	Fallback Holm + Enrichment (4/5,1/10,1/10) Zenrich=1	3%	19	78%/20%	18%/7%	50/61	52%/37%	71/81	70%/66%	101/111	82%	54%
	Fallback Holm + Enrichment (1/3,1/3,1/3) Zenrich=0	3%	19	94%/4%	11%/6%	50/61	50%/35%	71/81	78%/64%	101/111	81%	61%
	Fallback Holm + Enrichment (1/3,1/3,1/3) Zenrich=1	3%	19	78%/20%	9%/7%	50/61	41%/36%	71/81	65%/66%	101/111	80%	50%

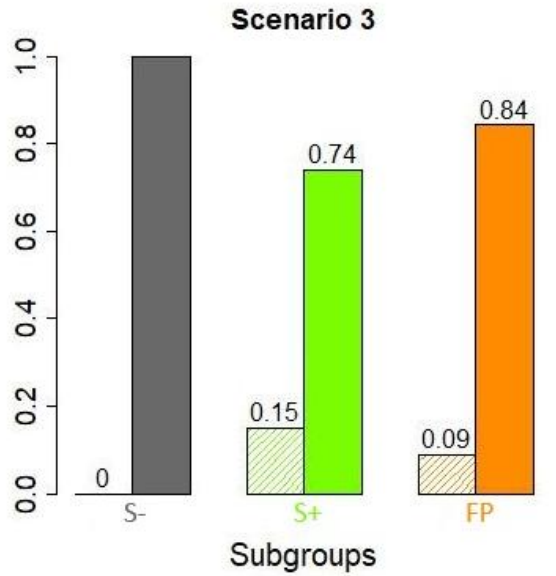
Scenario 2



- Summary for scenario 2:
  - In general, good percentage for any rejection
  - Best approaches for the rejection FP: hierarchical FP->S^+, Bonferroni, Holm, (Zhao, Enrichment, Enrichment+Holm) when α is favoring FP
  - For those approaches except enrichment, could reject both

		Phase 2 FA			Phase 3 IA-1		Phase 3 IA2		Phase 3 FA		TOTAL	
Scenario	Design	Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
Sc2	**Full pop**	1%	19	.	27%	50	70%	71	**90%**	101	90%	.
	Fallback Hierarchical S->FP	1%	19	.	10%/12%	50	42%/45%	71	70%/72%	101	72%	70%
	Fallback Hierarchical FP->S	1%	19	.	26%/10%	50	70%/32%	71	**90%**/42%	101	90%	42%
	Fallback Bonferroni	1%	19	.	16%/6%	50	58%/33%	71	**85%**/62%	101	86%	60%
	Fallback Holm	1%	19	.	17%/9%	50	60%/42%	71	**86%**/70%	101	86%	70%
	Fallback Zhao (0.6,0.4) a0=a/5	1%	19	.	16%/12%	50	55%/40%	71	81%/58%	101	82%	57%
	Fallback Zhao (0.6,0.4) a0=a/2	1%	19	.	21%/11%	50	62%/36%	71	**86%**/50%	101	87%	49%
	Fallback Zhao (0.6,0.4) a0=4a/5	1%	19	.	25%/11%	50	67%/33%	71	**89%**/45%	101	89%	44%
	Fallback Zhao with enrichment (0.75,0.25) a0=a/2	1%	19	.	18%/15%	53	58%/46%	73	**84%**/64%	103	88%	60%
	Enrichment (4/5,1/5) Zenrich=0	3%	19	93%/4%	22%/0%	50/61	62%/2%	71/81	**83%**/3%	101/111	86%	.
	Enrichment (4/5,1/5) Zenrich=1	3%	19	78%/20%	18%/1%	50/61	52%/7%	71/81	70%/14%	101/111	83%	.
	Enrichment (1/3,2/3) Zenrich=0	3%	19	93%/4%	11%/1%	50/61	49%/2%	71/81	77%/4%	101/111	80%	.
	Enrichment (1/3,2/3) Zenrich=1	3%	19	78%/20%	9%/3%	50/61	41%/11%	71/81	64%/16%	101/111	80%	.
	Fallback Holm + Enrichment (4/5,1/10,1/10) Zenrich=0	3%	19	94%/4%	22%/8%	50/61	63%/39%	71/81	**84%**/67%	101/111	86%	65%
	Fallback Holm + Enrichment (4/5,1/10,1/10) Zenrich=1	3%	19	78%/20%	18%/7%	50/61	52%/37%	71/81	70%/66%	101/111	82%	54%
	Fallback Holm + Enrichment (1/3,1/3,1/3) Zenrich=0	3%	19	94%/4%	11%/6%	50/61	50%/35%	71/81	78%/64%	101/111	81%	61%
	Fallback Holm + Enrichment (1/3,1/3,1/3) Zenrich=1	3%	19	78%/20%	9%/7%	50/61	41%/36%	71/81	65%/66%	101/111	80%	50%

Scenario 3



- Summary for scenario 3:
  - Best approaches to reject S^+: hierarchical S^+->FP, Holm, (Zhao, Enrichment, Enrichment+Holm) when α is favoring S^+ (56%-66%)
  - As we could expect, the best approaches to reject S^+ in scenario 3 are usually not the best to reject FP in scenario 2 (and vice versa) → no "best" approach although Holm performs well for both scenario
  - Assuming same trend in recruitment with S^+ only, timelines may be increased with enrichment (+16 months)

		Phase 2 FA			Phase 3 IA-1		IA2		FA		TOTAL	
Scenario	Design	Futility	Time	Select FP / S+	Power FP/S	Time	Cum Power FP/S	Time	Cum Power FP/S	Time	Global reject	Reject both
Sc3	Full pop	11%	19	.	5%	49	21%	68	41%	95	41%	.
	Fallback Hierarchical S->FP	11%	19	.	3%/10%	49	20%/39%	68	41%/**63%**	95	63%	41%
	Fallback Hierarchical FP->S	11%	19	.	5%/3%	49	22%/18%	68	44%/38%	95	44%	38%
	Fallback Bonferroni	11%	19	.	2%/5%	49	15%/28%	68	34%/54%	95	57%	32%
	Fallback Holm	11%	19	.	3%/5%	49	19%/29%	68	42%/**56%**	95	57%	40%
	Fallback Zhao (0.6,0.4) a0=a/5	11%	19	.	3%/10%	49	19%/37%	68	40%/**61%**	95	63%	39%
	Fallback Zhao (0.6,0.4) a0=a/2	11%	19	.	4%/8%	49	20%/33%	68	40%/**57%**	95	60%	37%
	Fallback Zhao (0.6,0.4) a0=4a/5	11%	19	.	4%/6%	49	20%/28%	68	41%/51%	95	56%	36%
	Fallback Zhao with enrichment (0.75,0.25) a0=a/2	11%	19	.	3%/11%	51	18%/42%	70	37%/**66%**	98	68%	35%
	Enrichment (4/5,1/5) Zenrich=0	10%	19	42%/48%	2%/3%	49/61	9%/18%	68/81	18%/34%	95/111	52%	.
	Enrichment (4/5,1/5) Zenrich=1	10%	19	16%/74%	1%/4%	49/61	3%/27%	68/81	7%/52%	95/111	59%	.
	Enrichment (1/3,2/3) Zenrich=0	10%	19	42%/48%	1%/8%	49/61	5%/27%	68/81	12%/40%	95/111	53%	.
	Enrichment (1/3,2/3) Zenrich=1	10%	19	16%/74%	0%/12%	49/61	2%/42%	68/81	5%/**62%**	95/111	67%	.
	Fallback Holm + Enrichment (4/5,1/10,1/10) Zenrich=0	10%	19	46%/44%	2%/3%	49/61	10%/22%	68/81	21%/51%	95/111	52%	20%
	Fallback Holm + Enrichment (4/5,1/10,1/10) Zenrich=1	10%	19	16%/74%	1%/2%	49/61	4%/23%	68/81	7%/54%	95/111	54%	7%
	Fallback Holm + Enrichment (1/3,1/3,1/3) Zenrich=0	10%	19	46%/44%	1%/6%	49/61	8%/32%	68/81	18%/**59%**	95/111	60%	18%
	Fallback Holm + Enrichment (1/3,1/3,1/3) Zenrich=1	10%	19	16%/74%	0%/7%	49/61	3%/37%	68/81	6%/**65%**	95/111	65%	6%

Conclusion

- Not all patients respond equally to the same treatment → Identifying these subgroups allows for targeted therapy, improving efficacy and reducing unnecessary toxicity
- Seamless Phase 2/3:
  - Reduces trial duration and patient recruitment phases, expediting clinical development
  - Possible adjustments at Phase 2 Transition including enrichment strategies
- No "best approach" in all scenarios → **compromise** between rejection of full population and subgroup
- Choose the strategy based on your **level of confidence in who may benefit**
  - If confident the treatment works in the full population, a simple design testing the full population is suitable
  - If confident the benefit is only in a subgroup, consider testing S^+ only
  - If uncertain, a combined or adaptive approach may offer a balanced and flexible solution

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Conclusion

- In our motivating example: high uncertainty on subgroup effect while we wanted to favor FP but consider S^+ → our simulation study showed:
  - (Bonferroni or) Holm is a very good option across all scenarios while statistically simple to implement
  - Zhao has good performance overall, even without enrichment (as increasing study prevalence may be complex in practice)
  - Enrichment + Holm is statistically much more complex for no real gain in performance

- In our motivating example, the effect of the population is in fact driven by the subgroup as we have a prevalence of 60%
  - If we keep the same scenario for the "global population" and decrease prevalence of S^+ to 20%, then subgroup effect will be very high but still a diluted in the population with a global effect in FP (tend to reject FP, difficult to identify subgroup effect)
  - If we keep the same effects in S^-/S^+ and decrease prevalence of S^+ to 20%: when only the subgroup responds performance are low as trial is not powered for that. Performance may be increased with enrichment but ⚠ futility and enrichment rules that highly impact performances (balance accross all scenarios).

- Project specific: need to consider prevalences and perform simulations on scenarios of interest

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Questions

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