Sequential Multiple Assignment Randomized Trial for COMparing Personalized Antibiotic StrategieS (SMART COMPASS): Design Considerations

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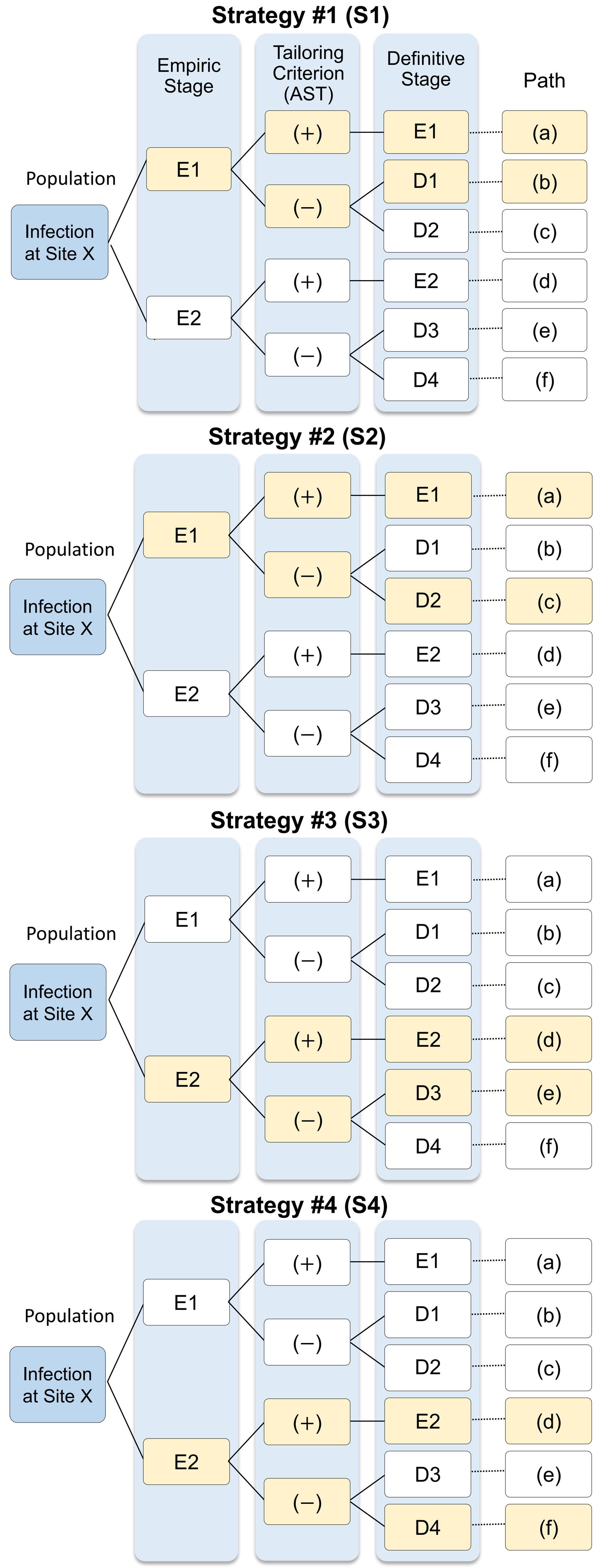
Introduction – Background and Research Objectives

- **A sequence of decisions with adjustment to therapy made over time in patients' management**- Adjustments tailored to individual patients as new information about those patients becomes available
- **Two therapeutic decision points in the treatment of serious bacterial infections**
  - **Empiric therapy**- selected based on the clinicians' best judgment given the immediately available and often limited information upon recognition of the clinical syndrome
  - **Definitive therapy**- selected once organism identification, antibiotic susceptibility testing (AST) results, tolerability, and clinical course of the patient are known
- **SMART COMPASS:** a pragmatic design, mirroring antibiotic treatment decision-making as they unfold in clinical practice and addressing the most relevant question for treating patients: **identification of the patient-management strategy that optimizes ultimate patient outcomes**

Research Questions		Example Hypotheses (Contrast of Interest)
Q1: Comparisons of empiric therapies coupled with subsequent therapies: relevant for clinicians triaging patients, making empiric therapy decisions without knowledge of definitive therapy options and decisions.		E1 is better than E2 under AST=S (paths (a) vs. (d))
Q2: Comparisons of definitive therapy conditioning on empiric therapy: relevant antibiotic drug developers as trials in the regulatory development paradigm comparing drugs		D1 is better than D2 (paths (b) vs. (c))
Q3: Comparisons of strategies: relevant for clinicians planning a sequential clinical course of treatment for patients	Pairwise strategy comparison	S1 is better than S2 (paths (a)+(b) vs. (a)+(c))
	Identification of best strategy	S1>S2>S3>S4 (paths (a)+(b) vs. (a)+(c) vs. (d)+(e) vs. (d)+(f))

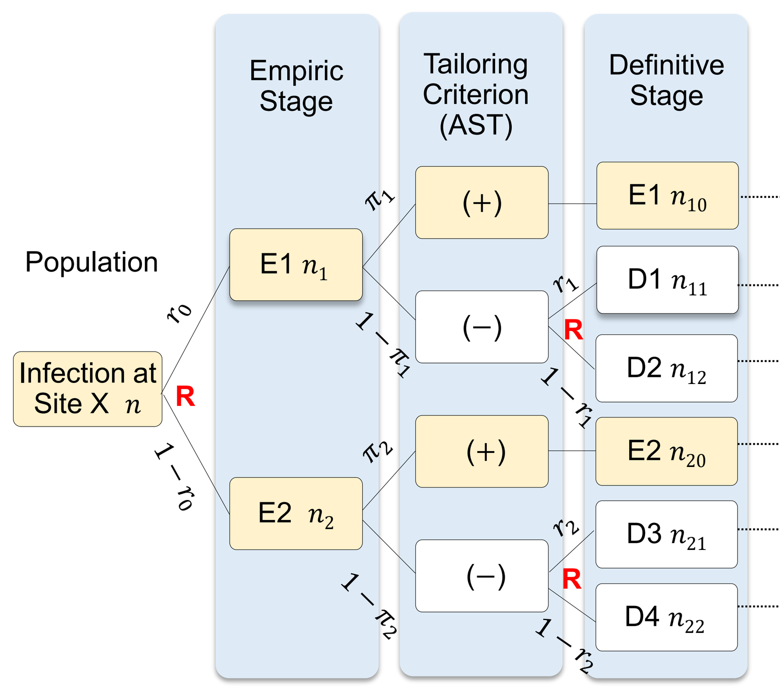
Example of SMART COMPSS Deigns



(+): S and tolerable; (−): Re or intolerable

Statistical Setting and Methodology Development

Statistical Settings



Path	Sample Size	Mean Parameter	Mean Estimate
(a)	$\pi_1 r_0 n$	μ_{10}	$\bar{Y}_{10}$
(b)	$(1-\pi_1)r_0 r_1 n$	μ_{11}	$\bar{Y}_{11}$
(c)	$(1-\pi_1)r_0(1-r_1)\, n$	μ_{12}	$\bar{Y}_{12}$
(d)	$\pi_2(1-r_0)\, n$	μ_{20}	$\bar{Y}_{20}$
(e)	$(1-\pi_2)(1-r_0)r_2 n$	μ_{21}	$\bar{Y}_{21}$
(f)	$(1-\pi_2)(1-r_0)(1-r_2)n$	μ_{22}	$\bar{Y}_{22}$

- Continuous endpoint
- known variance σ^2
- Known proportions π_1, π_2

Pairwise Strategy Comparison, Hypothesis, and Corresponding Parameter Estimates

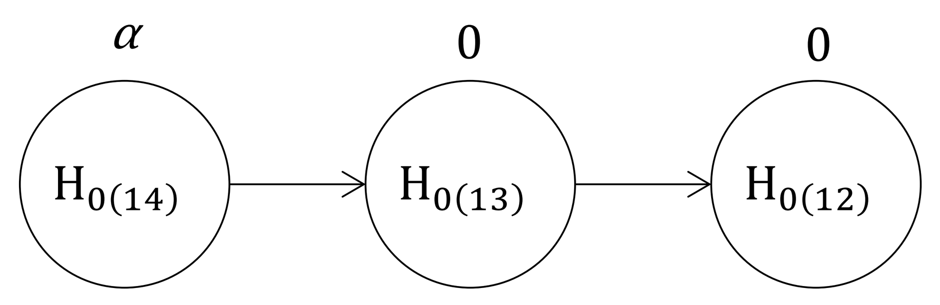
Strategy Comparison	Parameter	Hypothesis	$\hat{\delta}_{ij} = \hat{\mu}_{Si} - \hat{\mu}_{Sj}$
S1 vs. S2	$\delta_{12} = \mu_{S1} - \mu_{S2}$	H_0: $\delta_{12} \le 0$ VS H_1: $\delta_{12} > 0$	$\hat{\delta}_{12} = \frac{\pi_1\bar{Y}_{10} + r_1(1-\pi_1)\bar{Y}_{11}}{\pi_1 + r_1(1-\pi_1)} - \frac{\pi_1\bar{Y}_{10} + (1-r_1)(1-\pi_1)\bar{Y}_{12}}{\pi_1 + (1-r_1)(1-\pi_1)}$
S1 vs. S3	$\delta_{13} = \mu_{S1} - \mu_{S3}$	H_0: $\delta_{13} \le 0$ VS H_1: $\delta_{13} > 0$	$\hat{\delta}_{13} = \frac{\pi_1\bar{Y}_{10} + r_1(1-\pi_1)\bar{Y}_{11}}{\pi_1 + r_1(1-\pi_1)} - \frac{\pi_2\bar{Y}_{20} + r_2(1-\pi_2)\bar{Y}_{21}}{\pi_2 + r_2(1-\pi_2)}$
Strategy Comparison	**Test Statistic**	$\mathrm{E}[\hat{\delta}_{ij}]$	$\mathrm{Var}[\hat{\delta}_{ij}]$
S1 vs. S2	$Z_{12} = \frac{\hat{\delta}_{12}}{\mathrm{Var}[\hat{\delta}_{12}]}$	$\mathrm{E}[\hat{\delta}_{12}] = \frac{\pi_1\mu_{10} + r_1(1-\pi_1)\mu_{11}}{\pi_1 + r_1(1-\pi_1)} - \frac{\pi_1\mu_{10} + (1-r_1)(1-\pi_1)\mu_{12}}{\pi_1 + (1-r_1)(1-\pi_1)}$	$\mathrm{Var}[\hat{\delta}_{12}] = \frac{\sigma^2}{n}\left\{\frac{1-\pi_1}{r_0(\pi_1 + r_1(1-\pi_1))\,(\pi_1 + (1-r_1)(1-\pi_1))}\right\}$
S1 vs. S3	$Z_{13} = \frac{\hat{\delta}_{13}}{\mathrm{Var}[\hat{\delta}_{13}]}$	$\mathrm{E}[\hat{\delta}_{13}] = \frac{\pi_1\mu_{10} + r_1(1-\pi_1)\mu_{11}}{\pi_1 + r_1(1-\pi_1)} - \frac{\pi_2\mu_{20} + r_2(1-\pi_2)\mu_{21}}{\pi_2 + r_2(1-\pi_2)}$	$\mathrm{Var}[\hat{\delta}_{13}] = \frac{\sigma^2}{n}\left\{\frac{1}{r_0(\pi_1 + r_1(1-\pi_1))} + \frac{1}{(1-r_0)(\pi_2 + r_2(1-\pi_2))}\right\}$
Strategy Comparison	N_{ij}		N^*_{ij}
S1 vs. S2	$N_{12} = \begin{cases} N^*_{12}, & \text{if } N^*_{12} \text{ is integer,} \\ [N^*_{12}]+1, & \text{otherwise,} \end{cases}$		$N^*_{12} = \frac{\sigma^2(z_{1-\alpha}+z_{1-\beta})^2}{(\delta^*_{12})^2}\left\{\frac{1-\pi_1}{r_0(\pi_1 + r_1(1-\pi_1))\,(\pi_1 + (1-r_1)(1-\pi_1))}\right\}$
S1 vs. S3	$N_{13} = \begin{cases} N^*_{13}, & \text{if } N^*_{13} \text{ is integer,} \\ [N^*_{13}]+1, & \text{otherwise,} \end{cases}$		$N^*_{13} = \frac{\sigma^2(z_{1-\alpha}+z_{1-\beta})^2}{(\delta^*_{13})^2}\left\{\frac{1}{r_0(\pi_1 + r_1(1-\pi_1))} + \frac{1}{(1-r_0)(\pi_2 + r_2(1-\pi_2))}\right\}$

μ_{Si}: the mean of the strategy i, and estimated by weighting the paths' sample means; $i = 1,\ldots,4$; δ^*_{ij}: the clinically meaningful difference; $\delta_{ij} = \mu_{Si} - \mu_{Sj}$; $i,j = 1,\ldots 4, i \ne j$; N_{ij}: the total sample size required for the entire trial determined by the pairwise strategy comparison Si vs. Sj.

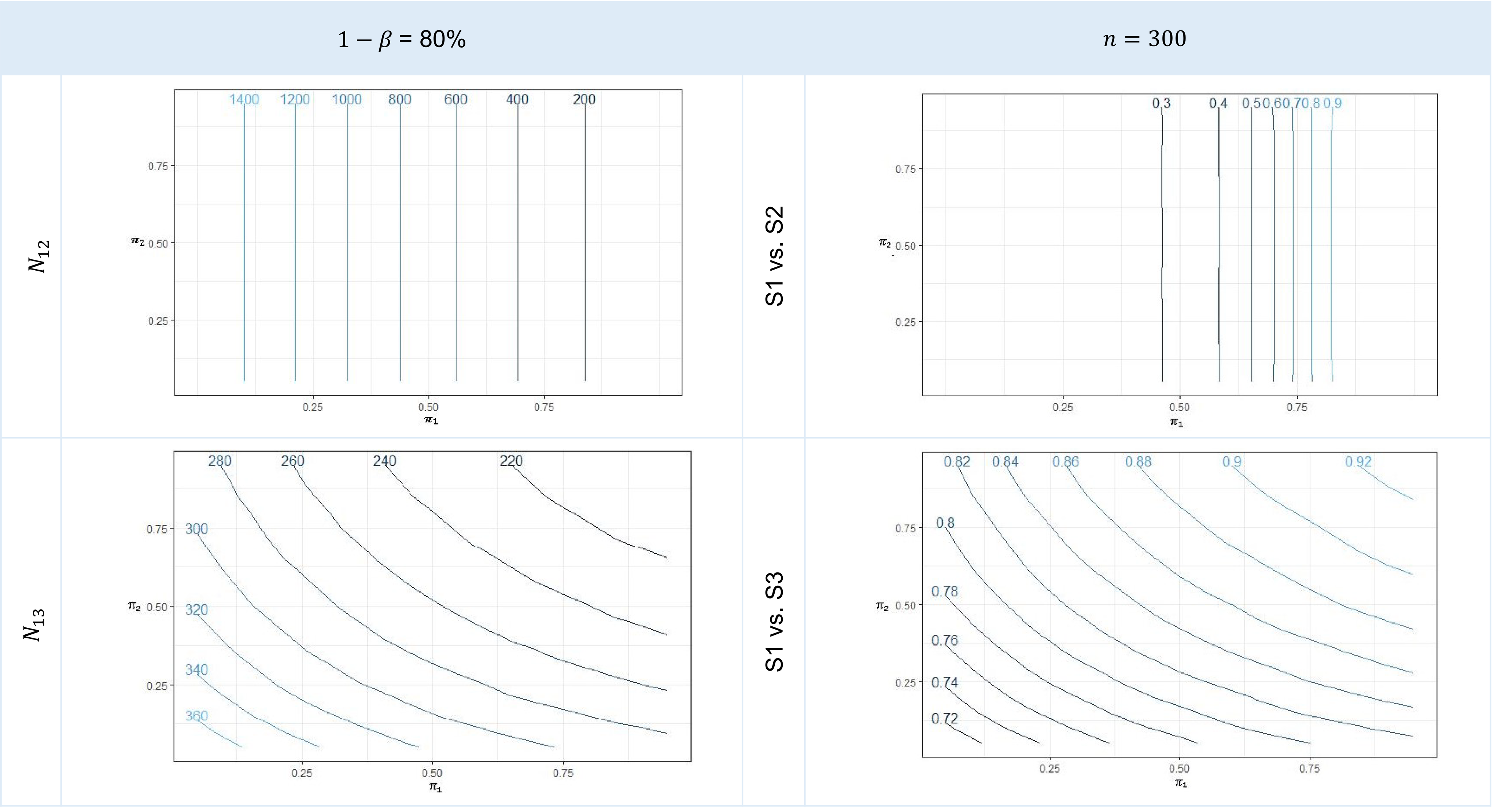
Procedure for Identifying the Best Strategy

Step 1: Order the estimated mean values $\hat{\mu}_{S(1)}, \hat{\mu}_{S(2)}, \hat{\mu}_{S(3)}$ and $\hat{\mu}_{S(4)}$, where $\hat{\mu}_{S(4)} < \hat{\mu}_{S(3)} < \hat{\mu}_{S(2)} < \hat{\mu}_{S(1)}$.

Step 2: Test each hypothesis with the order of $H_{0(14)} \to H_{0(13)} \to H_{0(12)}$ at the significance level of α as long as significant results are observed in all preceding tests.



Power and Sample Size Assessment via Simulation



π_1	π_2	n	Marginal Power			Conditional Power	
			$\Pr[H_{1(12)}]$	$\Pr[H_{1(13)}]$	$\Pr[H_{1(14)}]$	$\Pr[H_{1(13)} \mid H_{1(14)}]$	$\Pr[H_{1(12)} \mid H_{1(13)} \cap H_{1(14)}]$
0.1	0.1	1352	0.801	>0.999	>0.999	>0.999	0.801
	0.5	1352	0.800	>0.999	>0.999	>0.999	0.800
	0.9	1351	0.801	>0.999	>0.999	>0.999	0.801
0.5	0.1	691	0.803	0.986	>0.999	0.986	0.800
	0.5	684	0.801	0.995	>0.999	0.995	0.800
	0.9	683	0.802	0.997	>0.999	0.997	0.800
0.9	0.1	299	0.999	0.819	0.990	0.816	0.800
	0.5	241	0.993	0.811	0.989	0.810	0.804
	0.9	217	0.980	0.813	0.990	0.812	0.800

$r_0 = r_1 = r_2 = 0.5$; $\sigma^2 = 1$; $\mu_{10} = 1.0$, $\mu_{20} = 0.5$, $\mu_{S1} = 1.0$, $\mu_{S2} = 0.8$, $\mu_{S3} = 0.6$ and $\mu_{S4} = 0.4$. $\mu_{S(1)} = \mu_{S1}$, $\mu_{S(2)} = \mu_{S2}$, $\mu_{S(3)} = \mu_{S3}$ and $\mu_{S(4)} = \mu_{S4}$, and $\delta_{(12)} = \delta_{12} = 0.2$, $\delta_{(13)} = \delta_{13} = 0.4$ and $\delta_{(14)} = \delta_{14} = 0.6$.

Findings from Simulations

- **For pairwise comparisons,** when comparing S1 and S2, the required sample size N_{12} increases as π_1 goes to zero, but is unaffected by π_2 ← less "shared" participants (smaller π_1) decrease size of variance of $\hat{\delta}_{12}$.
- When comparing S1 with S3, the required sample size N_{13} increases as π_1 and/or π_2 go to zero ← the size of variance for $\hat{\delta}_{13}$ becomes larger with smaller π_1 and/or π_2.
- If π_1 is less than 0.6, the power to detect $\delta_{(12)}$ is smaller than that for $\delta_{(13)}$.
- **For identify the best strategy**, the required sample size n gradually deceases with higher π_1. Under the fixed π_1, n tends to be smaller with larger values of π_2. This tendency becomes clearer with higher π_1.