Synergy-Informed Design of Platform Trials for Combination Therapies

Nan Miles Xi [1], Man Mandy Jin [1], Lin Wang [2], Xin Huang [1]

[1] Data and Statistical Sciences, AbbVie Inc., North Chicago, IL 60064, USA

[2] Department of Statistics, Purdue University, West Lafayette, IN 47907, USA

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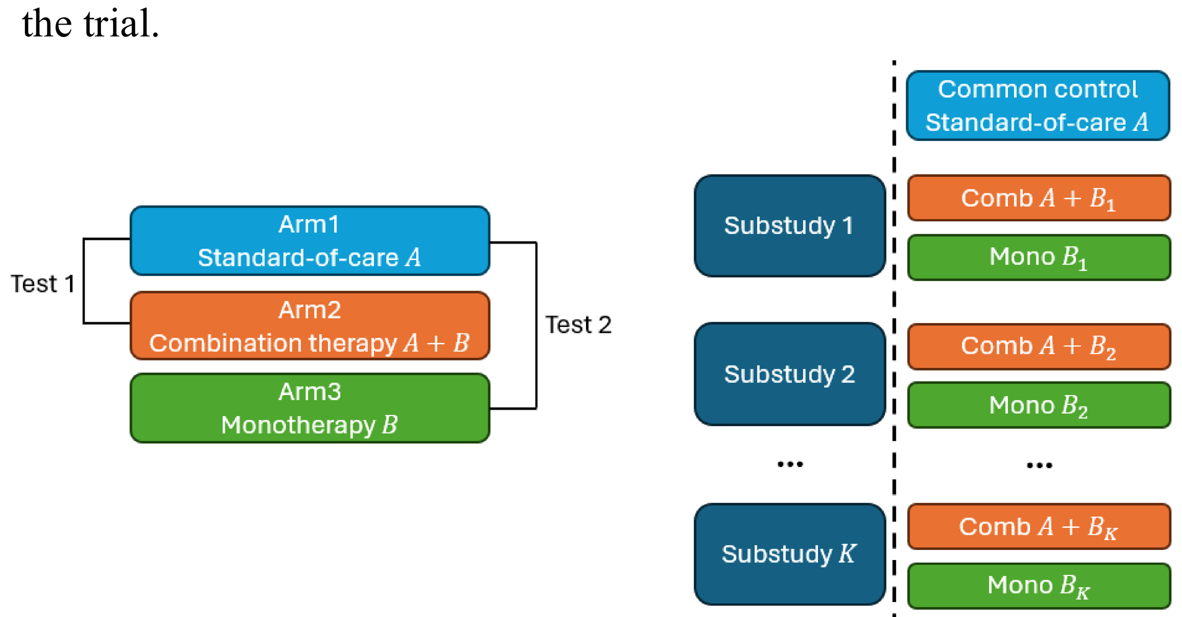
Introduction

Combination drug therapies hold significant promise for enhancing treatment efficacy, particularly in fields such as oncology, immunotherapy, and infectious diseases. However, designing clinical trials for these regimens poses unique statistical challenges due to multiple hypothesis testing, shared control groups, and overlapping treatment components that induce complex correlation structures. In this paper, we develop a novel statistical framework tailored for early-phase translational combination therapy trials, with a focus on platform trial designs. Our methodology introduces a generalized Dunnett's procedure that controls false positive rates by accounting for the correlations between treatment arms. Additionally, we propose strategies for power analysis and sample size optimization that leverage preclinical data to estimate effect sizes, synergy parameters, and inter-arm correlations. Simulation studies demonstrate that our approach not only controls various false positive metrics under diverse trial scenarios but also informs optimal allocation ratios to maximize power. A real-data application further illustrates the integration of translational preclinical insights into the clinical trial design process. An open-source R package is provided to support the application of our methods in practice. Overall, our framework offers statistically rigorous guidance for the design of early-phase combination therapy trials, aiming to enhance the efficiency of the bench-to-bedside transition.

Methodology

- ***False Positive Control***

We consider a platform trial design consisting of K substudies, where in each substudy, two investigational arms are compared against a common standard-of-care control arm A used throughout the trial.



For each substudy, we define two primary test statistics:

$$Z_{k,1} = \frac{\bar{Y}_{AB_k} - \bar{Y}_A}{\sqrt{Var(\bar{Y}_{AB_k} - \bar{Y}_A)}}, \quad Z_{k,2} = \frac{\bar{Y}_{B_k} - \bar{Y}_A}{\sqrt{Var(\bar{Y}_{B_k} - \bar{Y}_A)}}$$

Their correlation, $Cor(Z_{k,i}, Z_{l,j})$, is given by

$$Cor(Z_{k,i}, Z_{l,j}) = \frac{\frac{\rho_{(k,i),(l,j)}}{\sqrt{n_{k,i}n_{l,j}}} - \frac{\rho_{(k,i),A}}{\sqrt{n_{k,i}n_A}} - \frac{\rho_{(l,j),A}}{\sqrt{n_{l,j}n_A}} + \frac{1}{n_A}}{\sqrt{\left(\frac{1}{n_{k,i}} + \frac{1}{n_A} - 2\frac{\rho_{(k,i),A}}{\sqrt{n_{k,i}n_A}}\right)\left(\frac{1}{n_{l,j}} + \frac{1}{n_A} - 2\frac{\rho_{(l,j),A}}{\sqrt{n_{l,j}n_A}}\right)}}$$

We can compute each pairwise correlation to form a $2K \times 2K$ correlation matrix $\mathbf{\Sigma}$:

$$\mathbf{Z} = \left(Z_{1,1}, Z_{1,2}, Z_{2,1}, Z_{2,2}, \ldots, Z_{K,1}, Z_{K,2}\right)^{\mathrm{T}} \sim N(\mathbf{0}, \mathbf{\Sigma})$$

Given the $2K$-dimensional test statistic vector $\mathbf{Z}$ and its correlation matrix $\mathbf{\Sigma}$, to control the m-FWER at level α, we determine a critical value c^* such that

$$P\left(\sum_{k=1}^{K}\sum_{i=1}^{2} \mathbb{I}\{Z_{k,i} > c^*\} \geq m\right) = \alpha$$

- ***Allocation Ratio Optimization***

In each substudy k, there are three allocation ratios: p_A for the common control arm A, p_{B_k} for the monotherapy arm B_k, and p_{AB_k} for the combination arm $A + B_k$. Assume that each monotherapy B_k has a true effect δ_k over the standard-of-care A, defined as $\delta_k = \mu_{B_k} - \mu_A$. For the combination arm $A + B_k$, its effect is expressed as

$$\delta_{AB_k} = s_k \delta_k$$

where s_k is the *synergy parameter* in substudy k. Wald noncentrality parameters for the combination and monotherapy arms are given by:

$$W_{k,1} = \frac{N s_k^2 \delta_k^2}{\sigma^2\left(\frac{1}{p_{AB_k}} + \frac{1}{p_A} - 2\frac{\rho_{AB_k,A}}{\sqrt{p_{AB_k}p_A}}\right)}, W_{k,2} = \frac{N\delta_k^2}{\sigma^2\left(\frac{1}{p_A} + \frac{1}{p_{B_k}}\right)}$$

Let $\boldsymbol{\theta} = (\theta_0, \theta_1, \ldots, \theta_{2K})$ be a vector of unconstrained real parameters, and define:

$$p_A = \frac{\exp(\theta_0)}{\sum_{i=0}^{2K}\exp(\theta_i)}, p_{AB_k} = \frac{\exp(\theta_{2k-1})}{\sum_{i=0}^{2K}\exp(\theta_i)}, p_{B_k} = \frac{\exp(\theta_{2k})}{\sum_{k=0}^{2K}\exp(\theta_i)}$$

The optimization problem is then formulated as

$$\max_{\boldsymbol{\theta}} \min_{1 \leq k \leq K} \{W_{k,1}(\boldsymbol{\theta}), W_{k,2}(\boldsymbol{\theta})\}$$

- ***Sample Size Determination***

Step 1: Locating an upper bound

We estimate power at $N = N_0$ using the Monte Carlo evaluation described in Step 3. If the estimated power is below the target, we double the current N and repeat the evaluation. The first value of N meeting the power requirement is stored as N_{max}, and the previous value is recorded as N_{min}.

Step 2: Binary search

We initialize low $= N_{min}$ and high $= N_{max}$. While low $<$ high, we compute

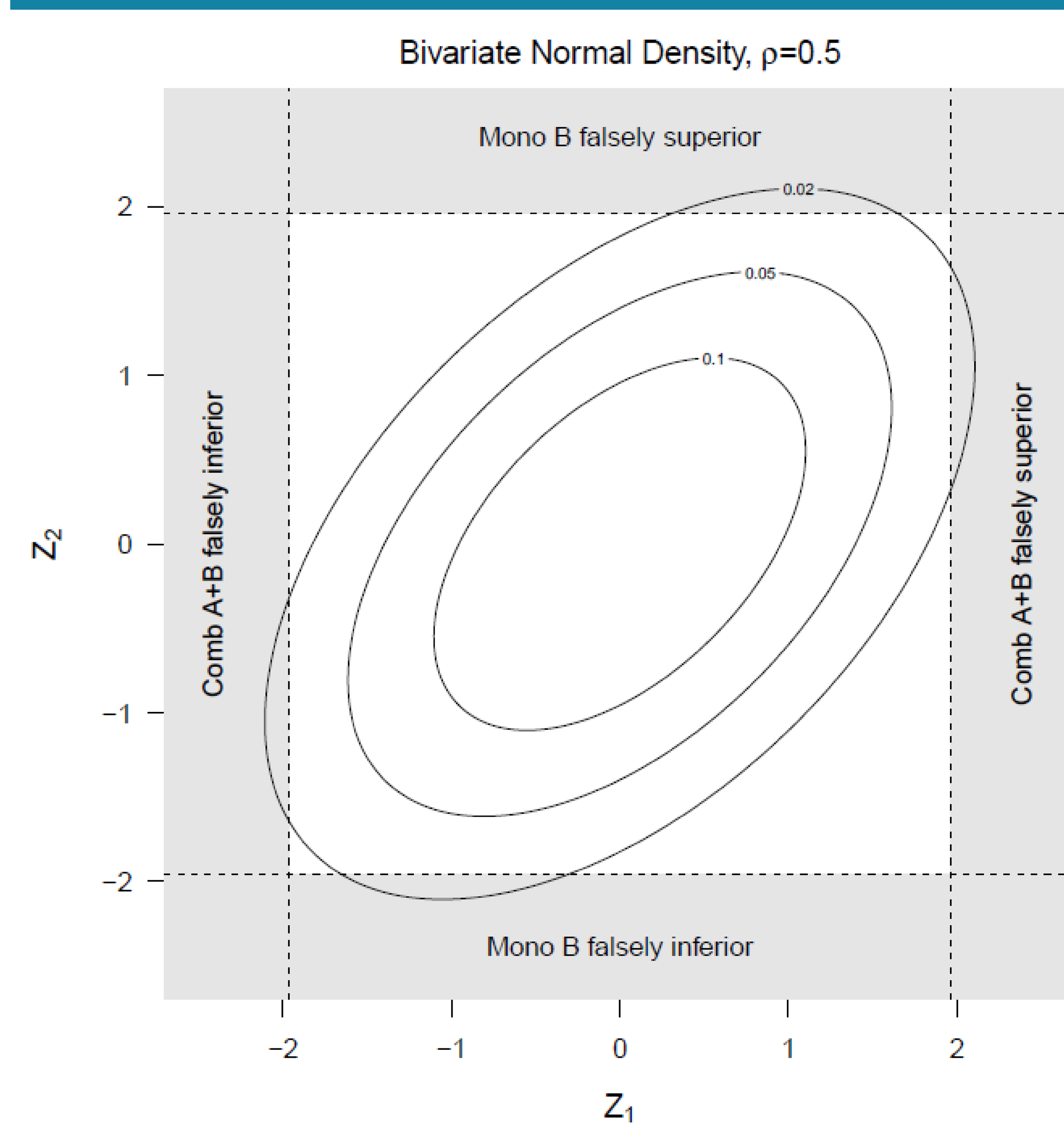
$$\text{mid} = \left\lfloor \frac{\text{low} + \text{high}}{2} \right\rfloor$$

and evaluate the power at $N =$ mid. If the estimated power is at least the target, we update high $=$ mid; otherwise, we set low $=$ mid $+ 1$. The algorithm terminates when low $=$ high, and this value is taken as the minimal sample size N^* that achieves the desired power.

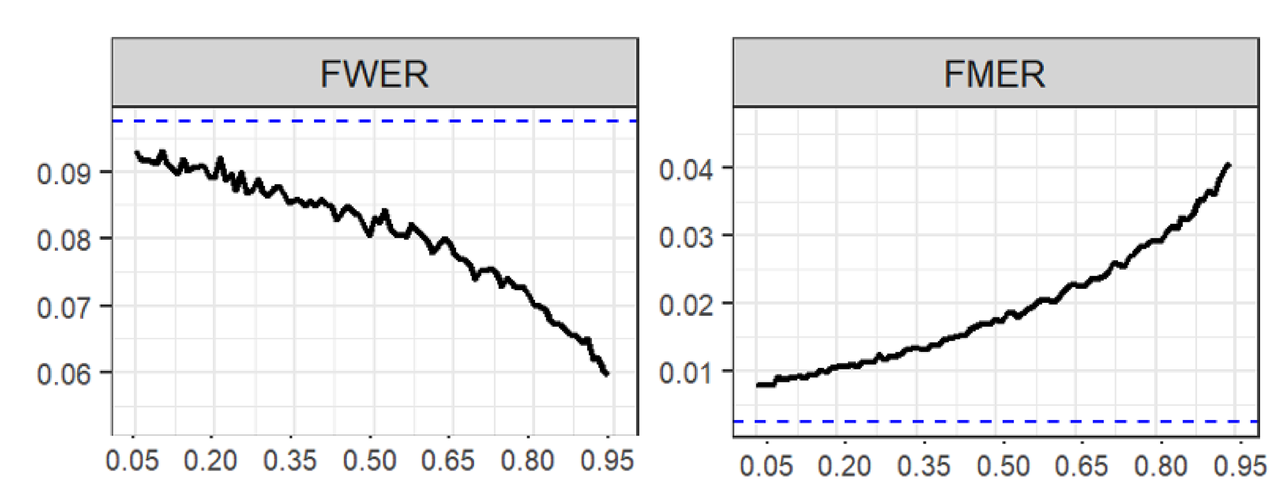
Step 3: Monte Carlo power evaluation

Given the sample size N, optimal allocation ratios (p_A^*, p_B^*, p_{AB}^*) and inter-arm correlations, we compute the correlation matrix $\mathbf{\Sigma}$. We then generate n_{sim} realizations of the sample means $(\bar{Y}_A, \bar{Y}_B, \bar{Y}_{AB})$, each drawn from their joint distribution. We compute the test statistics and count how many times exceed c^*. The minimum of the two empirical rejection proportions across simulations is taken as the estimated power for the given sample size N.

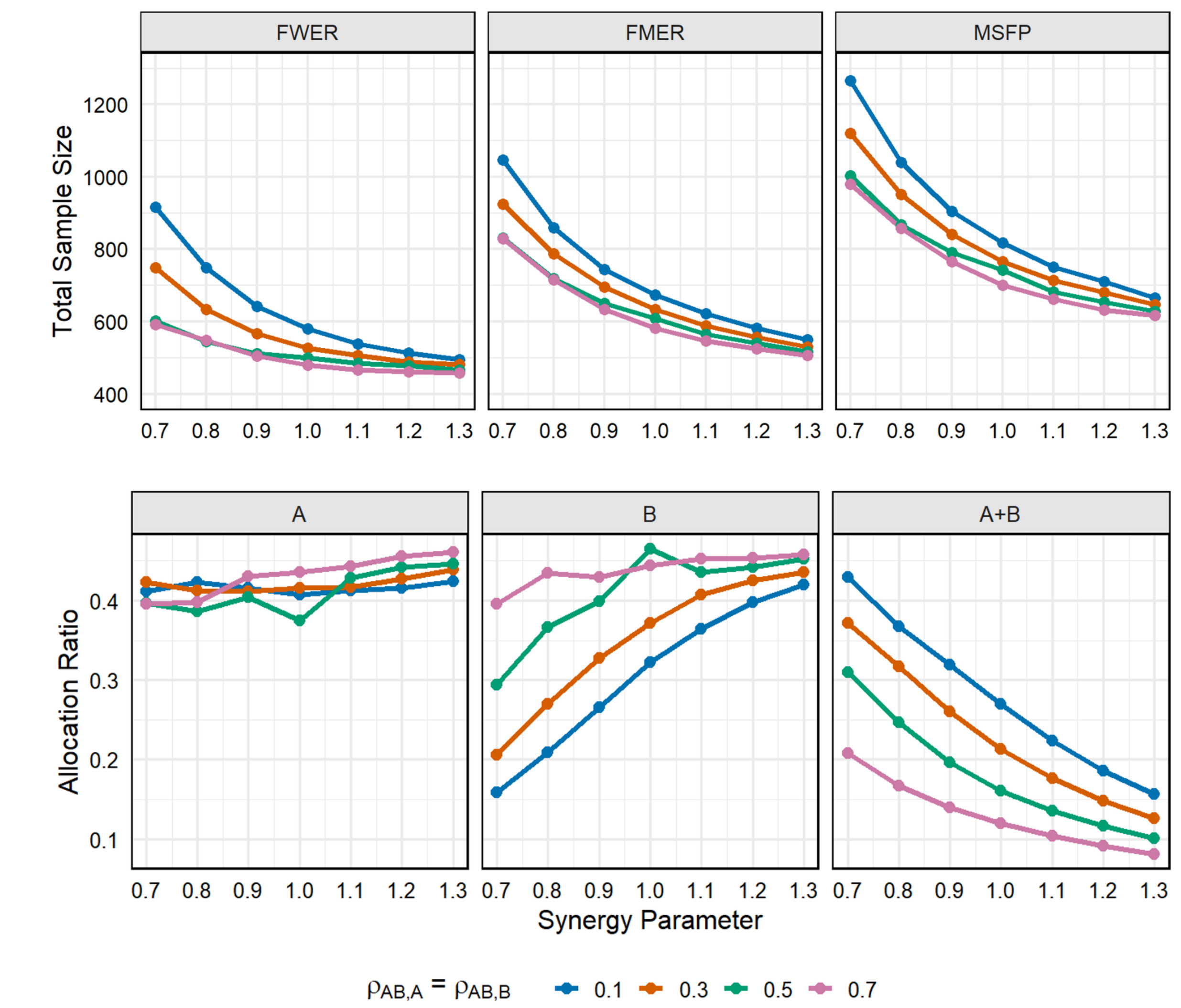
Results



Joint density functions of test statistics Z_1 and Z_2 under null hypothesis with correlation $\rho = 0.5$. The family-wise error rate (FWER) is defined as the sum of the four shaded edge regions minus the area of regions 1+2+3+4.



False positive metrics as functions of $\rho_{AB,B}$. The blue dashed lines represent baseline rates under an independent-trial design (FWER=0.0975; FMER=0.0025). All results are generated under the global null hypothesis at a significance level of $\alpha = 0.05$.



Optimal allocation ratios and required sample sizes under varied synergy and arm correlation scenarios.

A	B	p_A^*	p_B^*	p_{AB}^*	Error metric	p-value threshold	N^*
LEE011	everolimus	0.501	0.455	0.044	FWER	0.026	365
					FMER	0.026	365
					MSFP	0.006	443
LEE011	binimetinib	0.491	0.498	0.011	FWER	0.026	405
					FMER	0.029	397
					MSFP	0.007	479
INC280	trastuzumab	0.492	0.492	0.017	FWER	0.025	4746
					FMER	0.052	3938
					MSFP	0.013	4765
encorafenib	binimetinib	0.445	0.450	0.105	FWER	0.027	97
					FMER	0.013	114
					MSFP	0.003	135
BYL719	binimetinib	0.527	0.463	0.010	FWER	0.026	9321
					FMER	0.027	9239
					MSFP	0.006	11220
BKM120	binimetinib	0.527	0.462	0.011	FWER	0.025	52886
					FMER	0.042	46090
					MSFP	0.010	55412

Optimal allocation ratios and required sample sizes for six synthetic combination trials based on PDX preclinical data.

Conclusion

We present a synergy-aware statistical framework for designing platform trials in early-phase combination therapy studies. By generalizing Dunnett's procedure to account for shared controls and overlapping treatment components, our method rigorously controls multiple false-positive metrics while optimizing sample allocation and trial power. Through simulation and real preclinical data, we demonstrate how incorporating synergy estimates and correlation structures enables more efficient and statistically sound trial designs. **R package combodesign, source code and documentation are available from https://github.com/xnnba1984/combodesign.**