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SUPPLEMENTARY MATERIAL TO "MULTI-OBJECTIVE OPTIMAL DESIGNS IN COMPARATIVE CLINICAL TRIALS WITH COVARIATES: THE REINFORCED DOUBLY-ADAPTIVE BIASED COIN DESIGN"

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We provide an extension of inferential criteria **C1**-**C5** to the case of several covariates. From now on we assume the following notation: let $K \geq 2$ be the number of covariates taken into account and suppose that the kth covariate has (l_k+1) levels denoted by $0, 1, \ldots, l_k$, where 0 is the reference category ($k = 1, \ldots, K$). Thus we have $\prod_{k=1}^{K}(l_k + 1)$ strata and each of them can be represented by a K-dim vector $(c_1, \ldots, c_K)$, where c_k denotes the level of the kth covariate (with $c_k \in \{0, \ldots, l_k\}$ and $k = 1, \ldots, K$). At each stratum $(c_1, \ldots, c_K)$, let $N_n(c_1, \ldots, c_K)$ be the number of subjects within this stratum after n assignments, $\widetilde{N}_n(c_1, \ldots, c_K)$ denotes the number of allocations to A and $\pi_n(c_1, \ldots, c_K)$ is the corresponding proportion, where $\widetilde{N}_n(c_1, \ldots, c_K) = \pi_n(c_1, \ldots, c_K)N_n(c_1, \ldots, c_K)$. Let

$$\varrho_n(c_1, \ldots, c_K) = \{N_n(c_1, \ldots, c_K)\pi_n(c_1, \ldots, c_K)[1 - \pi_n(c_1, \ldots, c_K)]\}^{-1},$$

then inferential criteria **C1**-**C2** are given, respectively, by:

$$\det\left(\frac{\sigma^2}{n}\mathbf{M}^{-1}\right) = \sigma^{4+4p}\prod_{k=1}^{K}\prod_{c_k=0}^{l_k}\frac{\varrho_n(c_1, \ldots, c_K)}{N_n(c_1, \ldots, c_K)},$$

$$\det\left(\frac{\sigma^2}{n}\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D}\right) = \sigma^{4p}\left(\sum_{i=1}^{n}\delta_i\right)\left(n - \sum_{i=1}^{n}\delta_i\right)\prod_{k=1}^{K}\prod_{c_k=0}^{l_k}\frac{\varrho_n(c_1, \ldots, c_K)}{N_n(c_1, \ldots, c_K)}.$$

Letting now $\mathbb{K} = \{1, \ldots, l_1\} \otimes \{1, \ldots, l_2\} \otimes \ldots \otimes \{1, \ldots, l_K\}$ (in order to set for simplicity $\sum_{c_1=1}^{l_1}\sum_{c_2=1}^{l_2}\cdots\sum_{c_K=1}^{l_K} := \sum_{c_1,\ldots,c_K\in\mathbb{K}}$), criterion **C3** can be simplified as follows:

$$\operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{M}^{-1}\right) = \sigma^2\{\sum_{c_1,\ldots,c_K\in\mathbb{K}}\varrho_n(c_1, \ldots, c_K) +$$
$$\sum_{t=1}^{K}\sum_{1\leq i_1<i_2<\ldots<i_t\leq K}\prod_{h=1}^{t}(l_{i_h} + 1) \times \sum_{\substack{c_1, \ldots, c_K \in \mathbb{K} \\ c_{i_1} = \ldots = c_{i_t} = 0}}\varrho_n(c_1, \ldots, c_K)\},$$

where we use the convention that, if does not exist a multi-index $i_1, i_2, \ldots, i_t$ satisfying $i_1 < i_2 < \ldots < i_t$, then the corresponding term of the sum is treated as zero. The rationality of this formula is the following: each stratum $(c_1, \ldots, c_K) \in \mathbb{K}$ (which does not involve any of the reference categories of the covariates) gives its contribution $\varrho_n(c_1, \ldots, c_K)$ with weight equal to 1, whereas the contribution of every stratum involving the reference category of one or more covariates is weighed by the product of the number of levels of the covariates that are fixed to their reference categories (for $t = 1$ we sum over the strata with exactly one covariate at the reference category, for $t = 2$ the sum is over all the strata with a pair of factors fixed at their reference levels, etc...).

Moreover, criterion $\mathbf{C4}$ coincides with $\mathbf{C5}$ and is given by

$$\operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D}\right) = \operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{E}^t\mathbf{M}^{-1}\mathbf{E}\right) = \operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{M}^{-1}\right) - \sigma^2\varrho_n(0, \ldots, 0).$$

Sketch of the proof. The proof follows directly from those in Appendix A.1 generalized to the case of $K \geq 2$ covariates. Taking into account criterion **C1**, let $(Z_1, \ldots, Z_K)$ be the vector of covariates of interest, where each Z_k is represented by a l_k-dim vector $\mathbb{Z}_k$ of dummy variables ($k = 1 \ldots, K$). Now $\boldsymbol{\delta}^t\mathbf{F}$ contains the number of allocations to A at each level of every covariate (except the reference categories), as well as at each interaction of every order among covariates, namely $\boldsymbol{\delta}^t\mathbf{F} = (\widetilde{\mathbf{N}}^t_{\mathbb{Z}_1}, \ldots, \widetilde{\mathbf{N}}^t_{\mathbb{Z}_K}, \widetilde{\mathbf{N}}^t_{\mathbb{Z}_1\otimes\mathbb{Z}_2}, \ldots, \widetilde{\mathbf{N}}^t_{\mathbb{Z}_1\otimes\mathbb{Z}_2\otimes\ldots\mathbb{Z}_K})$. Using the same partition of the matrix $\boldsymbol{\Omega}_A$ given in equation (A.1) with $\mathbf{C} = \operatorname{diag}(\widetilde{\mathbf{N}}_{\mathbb{Z}_1\otimes\mathbb{Z}_2\otimes\ldots\mathbb{Z}_K})$ (whereas matrices $\mathbf{A}$ and $\mathbf{B}$ must be rearranged accordingly), then

$$\det\mathbf{C} = \prod_{c_1,\ldots,c_K\in\mathbb{K}} \widetilde{N}_n(c_1, \ldots, c_K)$$

and

$$\det(\mathbf{A} - \mathbf{B}\mathbf{C}^{-1}\mathbf{B}^t) = \prod_{t=1}^{K-1} \prod_{1\leq i_1<i_2<\ldots<i_t\leq K} \prod_{\substack{c_1, \ldots, c_K \in \mathbb{K} \\ c_{i_1} = \ldots = c_{i_t} = 0}} \widetilde{N}_n(c_1, \ldots, c_K)\,,$$

that involves the products of the terms $\widetilde{N}_n(c_1, \ldots, c_K)$'s at each stratum with at least one covariate in the reference category, except stratum $(0, \ldots, 0)$. Since $\sum_{i=1}^n \delta_i - \boldsymbol{\delta}^t\mathbf{F}(\boldsymbol{\Omega}_A)^{-1}\mathbf{F}^t\boldsymbol{\delta} = \widetilde{N}_n(0, \ldots, 0)$, thus criterion **C1** follows directly. Inferential criteria **C2**-**C5** can be derived analogously, after tedious calculations.

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