The Annals of Statistics
2012, Vol. 40, No. 3, 1315–1345
DOI: 10.1214/12-AOS1007

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

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The present paper deals with the problem of allocating patients to two competing treatments in the presence of covariates or prognostic factors in order to achieve a good trade-off among ethical concerns, inferential precision and randomness in the treatment allocations. In particular we suggest a multipurpose design methodology that combines efficiency and ethical gain when the linear homoscedastic model with both treatment/covariate interactions and interactions among covariates is adopted. The ensuing compound optimal allocations of the treatments depend on the covariates and their distribution on the population of interest, as well as on the unknown parameters of the model. Therefore, we introduce the reinforced doubly adaptive biased coin design, namely a general class of covariate-adjusted response-adaptive procedures that includes both continuous and discontinuous randomization functions, aimed to target any desired allocation proportion. The properties of this proposal are described both theoretically and through simulations.

1. Introduction. In the medical profession physicians are expected to act in the best interests of each patient under their care, but in clinical trials the patients are statistical units in an experiment, and the demands of individual care and experimental information often come into conflict. Thus the ensuing ethical problem is how to balance the welfare of the patients in the trial against a possible knowledge gain that will improve the care of future patients. In experimental medicine it is commonly believed that randomized trials are the answer, especially in the case of Phase III clinical trials, where the aim is to compare the efficacy of two available treatments and patients are sequentially randomized to one of them. In this context, several design methodologies have been recently proposed in order to derive suitable target allocations of the treatments that represent a compromise between ethical demands and inferential goals [4, 17, 22]. These targets depend in general on the unknown model parameters and can be implemented by adopting suitable response-adaptive procedures, such as the sequential maximum likelihood design [15], the doubly adaptive biased coin design [13] and the efficient randomized-adaptive design (ERADE) [14], converging to them.

An additional peculiarity of Phase III trials is that they usually involve some set of important prognostic factors or covariates. The role of these factors may be

Received March 2012.
MSC2010 subject classifications. Primary 62K05, 62L05; secondary 62G20, 60F05.
Key words and phrases. Balance, information criteria, ethics, CARA designs.

crucial in order to derive correct inferential conclusions about the treatment effects and this is one of the reasons for which taking into account the covariates has now become of primary importance not only from an inferential point of view but also from a design perspective (for a recent literature [2, 5, 18, 20]).

In the last decade there has been a growing statistical interest in the topic of adaptive designs adjusted for covariates and, in particular, in covariate-adjusted response-adaptive (CARA) randomization methods; see [12, 19, 23]. This is a class of sequential allocation procedures that modifies the probabilities of treatment assignments on the basis of the available information—that is, earlier responses and allocations, past covariate profiles and the covariate information of the present patient—with the aim of skewing the allocations towards the treatment that appears to be superior or, more generally, of converging to a desired target that should incorporate inferential demands related to optimal inference about the treatment effects and, eventually, ethical concerns.

Even if in the presence of prognostic factors the inferential methods, as well as the ethical goals, change on the basis of the nature of the responses and the covariates, the design literature has essentially focused on the simplified scenario of absence of treatment/covariate interactions; see, for instance, [3, 7, 8]. In this context, the relative performance of the treatments is the same for every subject's profile, so that the ethical demand simply consists of allocating the best treatment to as many patients as possible, independently on their covariates. This also explains the absence of methodological proposals through which one can derive target allocations that, by incorporating both inferential and ethical considerations, depend on the covariates. Whereas, in the more complex scenario of treatment/covariate interactions, the covariates play a fundamental role also from an ethical viewpoint, since the superiority/inferiority of a given treatment, as well as the discrepancy between the treatment effects, depend on the subject's profiles.

Therefore, one of the primary aims of the present paper consists of analyzing, from a design perspective, the linear model with both treatment/covariate interactions and interactions among covariates, in terms of ethical impact as well as inferential efficiency. After deriving the analytical expressions of the most popular information criteria, we propose a multipurpose design strategy based on a compound optimization approach, that combines inferential precision and ethical gain by means of flexible weights, which can be fixed a priori by the experimenter, or they may be functions of the unknown model parameters.

This multipurpose criterion leads to a locally optimal allocation which depends, in general, on the covariates and their population distribution, as well as on the unknown model parameters, and allows to promote for every profile a suitable compromise between information and ethical demands. Furthermore, we introduce the reinforced doubly adaptive biased coin design (RDBCD), namely a new class of CARA procedures that generalizes some earlier works [1, 23] and also extends several procedures proposed in the literature, such as the doubly adaptive biased coin design and the ERADE, to the covariate setting. The RDBCD, which admits

both continuous and discontinuous randomization functions, can target any desired allocation proportion, allowing also to force closeness to the chosen target in an appropriate way, while maintaining randomization. We show, both theoretically and through simulations, that the proposed procedure has desirable properties, asymptotically and, in particular, for small samples.

The paper is structured as follows. Starting from the notation in Section 2, Sections 3 and 4 deal with the optimal designs for inference and ethics, respectively. Section 5 describes the combined approach, while the properties of the ensuing optimal compound target are discussed in Section 6. In Section 7 we introduce the RDBCD, showing its asymptotic properties as well as the asymptotic inference related to the adoption of such a procedure. Section 8 deals with some finite sample comparisons between our proposal and some of the fundamental procedures proposed in the literature. We end the paper with a brief discussion in Section 9.

Motivated by the clinical practice, the present paper takes into account categorical covariates, since in the large majority of real Phase III clinical trials the prognostic factors are polytomous and, even if quantitative, they are often categorized by adopting suitable thresholds. Furthermore, for ease of notation we deal with just two covariates, but the extension to the case of several factors is straightforward (see [6]).

2. The linear model with covariates. Let A and B be two competing treatments. We suppose that for each subject entering the trial we observe a vector $\mathbf{Z}$ of concomitant categorical variables. Moreover, we assume the covariates to be random, that is, they are not under the experimenters' control when the subjects turn up for the trial, but they can be measured before assigning a treatment. Then the treatments are assigned according to a given randomization rule, with δ an indicator variable such that $\delta = 1$ or 0 if the subject is assigned to A or B, respectively, and an outcome Y is observed. Conditionally on the covariates and the treatments, patients' responses are assumed to be independent. A common model for the response that accounts for treatment/covariate interactions is the following linear homoscedastic model:

$$\begin{aligned} E(Y_i) &= \delta_i \mu_A + (1-\delta_i)\mu_B + \mathbf{f}(\mathbf{z}_i)^t\big(\delta_i \boldsymbol{\beta}_A + (1-\delta_i)\boldsymbol{\beta}_B\big), \\ V(Y_i) &= \sigma^2, \qquad i = 1, \ldots, n, \end{aligned} \tag{2.1}$$

where Y_i is the outcome of the ith subject, μ_A and μ_B are the baseline treatment effects, $\mathbf{f}(\cdot)$ is a known vector function, $\mathbf{z}_i$ is the vector of covariates observed on the ith individual and $\boldsymbol{\beta}_A, \boldsymbol{\beta}_B$ are p-dim vectors of possibly different regression parameters related to A and B, respectively. Under this model $\mu_A, \mu_B, \boldsymbol{\beta}_A$ and $\boldsymbol{\beta}_B$ are of interest since the relative performance of the treatments depends on the patient's covariates. Indeed, for any given covariate profile $\mathbf{z}_i$, we obtain

$$\begin{aligned} \theta(\mathbf{z}_i) &= E(Y_i \mid \delta_i = 1, \mathbf{Z}_i = \mathbf{z}_i) - E(Y_i \mid \delta_i = 0, \mathbf{Z}_i = \mathbf{z}_i) \\ &= \mu_A - \mu_B + \mathbf{f}(\mathbf{z}_i)^t(\boldsymbol{\beta}_A - \boldsymbol{\beta}_B) = \alpha + \mathbf{f}(\mathbf{z}_i)^t\boldsymbol{\tau}. \end{aligned} \tag{2.2}$$

After n assignments, let $\mathbf{F} = (\mathbf{f}(\mathbf{z})^t)_{n\times p}$, $\boldsymbol{\delta}_n = (\delta_1, \ldots, \delta_n)^t$, $\boldsymbol{\Delta}_n = \operatorname{diag}(\boldsymbol{\delta}_n)$ and $\mathbf{X} = [\boldsymbol{\delta}_n : \mathbf{1}_n - \boldsymbol{\delta}_n : \boldsymbol{\Delta}_n\mathbf{F} : (\mathbf{I}_n - \boldsymbol{\Delta}_n)\mathbf{F}]$, where $\mathbf{1}_n$ and $\mathbf{I}_n$ are the n-dim vector of ones and the n-dim identity matrix, respectively. Moreover, let $\hat{\boldsymbol{\gamma}}_n = (\hat{\mu}_A, \hat{\mu}_B, \hat{\boldsymbol{\beta}}_A^t, \hat{\boldsymbol{\beta}}_B^t)^t$ be the least square estimator of $\boldsymbol{\gamma} = (\mu_A, \mu_B, \boldsymbol{\beta}_A^t, \boldsymbol{\beta}_B^t)^t$, then if $(\mathbf{X}^t\mathbf{X})^{-1}$ exists, the variance–covariance matrix is

$$V(\hat{\boldsymbol{\gamma}}_n) = \sigma^2(\mathbf{X}^t\mathbf{X})^{-1} = n^{-1}\sigma^2\mathbf{M}^{-1},$$

where $\mathbf{M}$ is the $(2+2p)$-dim average (*per observation*) information matrix

$$\mathbf{M} = \frac{1}{n}\begin{pmatrix} \sum_{i=1}^n \delta_i & 0 & \boldsymbol{\delta}_n^t\mathbf{F} & \mathbf{0}_{1\times p} \\ 0 & n - \sum_{i=1}^n \delta_i & \mathbf{0}_{1\times p} & (\mathbf{1}_n - \boldsymbol{\delta}_n)^t\mathbf{F} \\ \mathbf{F}^t\boldsymbol{\delta}_n & \mathbf{0}_{p\times 1} & \mathbf{F}^t\boldsymbol{\Delta}_n\mathbf{F} & \mathbf{0}_{p\times p} \\ \mathbf{0}_{p\times 1} & \mathbf{F}^t(\mathbf{1}_n - \boldsymbol{\delta}_n) & \mathbf{0}_{p\times p} & \mathbf{F}^t(\mathbf{I}_n - \boldsymbol{\Delta}_n)\mathbf{F} \end{pmatrix}. \tag{2.3}$$

REMARK 2.1. In the absence of treatment/covariate interactions $\boldsymbol{\beta}_A = \boldsymbol{\beta}_B = \boldsymbol{\beta}$, that is, $\boldsymbol{\tau} = \mathbf{0}$, and the homoscedastic model (2.1) becomes

$$E(Y_i) = \delta_i\mu_A + (1-\delta_i)\mu_B + \mathbf{f}(\mathbf{z}_i)^t\boldsymbol{\beta}, \qquad i = 1, \ldots, n. \tag{2.4}$$

In this case, it is customary to regard $\boldsymbol{\beta}$ as a nuisance parameter, since from (2.2) $\theta(\mathbf{z}_i) = \mu_A - \mu_B$ for any given covariate profile $\mathbf{z}_i$, so that the inferential interest typically lies in estimating μ_A and μ_B, or $\mu_A - \mu_B$, as precisely as possible.

3. Inferential optimality and balanced designs. In order to avoid cumbersome notation, from now on we assume, without loss of generality, only two categorical covariates, that is, $\mathbf{Z} = (T, W)$. Suppose that T is categorized into levels $t_0, t_1, \ldots, t_J$ and let $w_0, w_1, \ldots, w_L$ be the levels of W, so that T and W can be represented by a J-dimensional vector $\mathbb{T}$ and a L-dimensional vector $\mathbb{W}$ of dummy variables, respectively, where t_0 and w_0 are the reference categories. Assume that $\{Z_i, i \geq 1\}$ is a sequence of i.i.d. random vectors, where each Z_i is distributed in the population according to $\Pr\{Z_i = (t_j, w_l)\} = p(j,l) > 0$ $(j = 0, \ldots, J; l = 0 \ldots, L)$, where $\sum_{j=0}^J \sum_{l=0}^L p(j,l) = 1$. Moreover, in order to account for the general situation of both treatment/covariate interactions and interaction among covariates in the rest of the paper, we let

$$\mathbf{f}^t(\mathbf{z}) = (\mathbb{T}^t, \mathbb{W}^t, \mathbb{T}^t \otimes \mathbb{W}^t), \tag{3.1}$$

that is, $\mathbf{f}(\cdot)$ is the p-dim vector including all interaction effects, with $p = J + L + J \cdot L$.

At the end of a trial with n assignments, let $N_n(j,l) = \sum_{i=1}^n \mathbb{1}_{\{Z_i = (t_j, w_l)\}}$ be the number of subjects within the stratum (t_j, w_l), where $\mathbb{1}_{\{\cdot\}}$ represents the indicator function, $\widetilde{N}_n(j,l) = \sum_{i=1}^n \delta_i \mathbb{1}_{\{Z_i = (t_j, w_l)\}}$ the number of allocations

to A within this stratum and $\pi_n(j,l)$ the corresponding proportion, that is, $\pi_n(j,l) = N_n(j,l)^{-1}\widetilde{N}_n(j,l)$, for any $j = 0,\dots,J$ and $l = 0,\dots,L$. Moreover, let $\mathbf{N}_n = \{N_n(j,l) : j = 0,\dots,J; l = 0,\dots,L\}$ and $\boldsymbol{\pi}_n = \{\pi_n(j,l) : j = 0,\dots,J; l = 0,\dots,L\}$.

Adopting model (2.1), the design for optimal inference consists in allocating the treatments so as to minimize one of the following criteria:

C1 $\det V(\hat{\boldsymbol{\gamma}}_n) = \det(n^{-1}\sigma^2\mathbf{M}^{-1})$;

C2 $\det V\binom{\hat{\boldsymbol{\beta}}_A}{\hat{\boldsymbol{\beta}}_B} = \det(n^{-1}\sigma^2\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D})$, where $\mathbf{D}^t = (\mathbf{0}_{2p\times 2} : \mathbf{I}_{2p})$;

C3 $\operatorname{tr} V(\hat{\boldsymbol{\gamma}}_n) = \operatorname{tr}(n^{-1}\sigma^2\mathbf{M}^{-1})$;

C4 $\operatorname{tr} V\binom{\hat{\boldsymbol{\beta}}_A}{\hat{\boldsymbol{\beta}}_B} = \operatorname{tr}(n^{-1}\sigma^2\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D})$;

C5 $\operatorname{tr} V(\hat{\boldsymbol{\beta}}_A - \hat{\boldsymbol{\beta}}_B) = \operatorname{tr}(n^{-1}\sigma^2\mathbf{E}^t\mathbf{M}^{-1}\mathbf{E})$, $\mathbf{E}^t = (\mathbf{0}_{p\times 2} : \mathbf{I}_p : -\mathbf{I}_p)$

with $\mathbf{M}^{-1}$ replaced by the Moore–Penrose inverse, if needed. It is easy to check that C1–C5 are convex functions of $\mathbf{M}$, invariant with respect to permutations of the bottom two block rows and the two right-hand block columns of $\mathbf{M}$.

For given covariates, the jointly balanced design

$$\boldsymbol{\pi}_I^* = \{\pi_I^*(j,l) = 1/2, \text{ for any } j = 0,\dots,J \text{ and } l = 0,\dots,L\}, \tag{3.2}$$

is optimal for model (2.1) with respect to any criterion Φ_I of the information matrix $\mathbf{M}$, which is convex and invariant w.r.t. permutations of the bottom two block rows and the two right-hand block columns, as well as the first two rows and columns. To see this, it is straightforward to check that assuming (3.2) the ensuing information matrix

$$\mathbf{M}^* = \frac{1}{2n}\begin{pmatrix} n & 0 & \mathbf{1}_n^t\mathbf{F} & \mathbf{0}_{1\times p} \\ 0 & n & \mathbf{0}_{1\times p} & \mathbf{1}_n^t\mathbf{F} \\ \mathbf{F}^t\mathbf{1}_n & \mathbf{0}_{p\times 1} & \mathbf{F}^t\mathbf{F} & \mathbf{0}_{p\times p} \\ \mathbf{0}_{p\times 1} & \mathbf{F}^t\mathbf{1}_n & \mathbf{0}_{p\times p} & \mathbf{F}^t\mathbf{F} \end{pmatrix} \tag{3.3}$$

is invariant w.r.t. permutations of the bottom two block rows and the two right-hand block columns, as well as the first two rows and columns. For any information matrix $\mathbf{M}$ of the type (2.3), by the simultaneous permutation of the first two rows and two columns as well as the bottom two block rows and the two right-hand block columns, we get the information matrix $\tilde{\mathbf{M}}$ corresponding to the design which switches treatments A and B. Clearly $\Phi_I(\tilde{\mathbf{M}}) = \Phi_I(\mathbf{M})$, $(\mathbf{M} + \tilde{\mathbf{M}})/2 = \mathbf{M}^*$ and then by convexity

$$\Phi_I(\mathbf{M}^*) = \Phi_I\big(\tfrac{1}{2}(\mathbf{M} + \tilde{\mathbf{M}})\big) \le \tfrac{1}{2}[\Phi_I(\mathbf{M}) + \Phi_I(\tilde{\mathbf{M}})] = \Phi_I(\mathbf{M}).$$

Note that, independently on the presence or absence of treatment/covariate interactions, the jointly balanced allocation (3.2) is still optimal, even in the absence of interactions among covariates; see [5] for a detailed discussion.

PROPOSITION 3.1. *Assuming model* (2.1) *with* (3.1), *inferential criteria* C1–C5 *can be simplified as follows*:

$$\text{C1:}\quad \det\left(\frac{\sigma^2}{n}\mathbf{M}^{-1}\right) = \frac{\sigma^{4+4p}}{\prod_{j=0}^{J}\prod_{l=0}^{L}\pi_n(j,l)[1-\pi_n(j,l)]N_n(j,l)^2}, \tag{3.4}$$

$$\text{C2:}\quad \det\left(\frac{\sigma^2}{n}\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D}\right) = \frac{(\sum_{i=1}^{n}\delta_i)(n-\sum_{i=1}^{n}\delta_i)\sigma^{4p}}{\prod_{j=0}^{J}\prod_{l=0}^{L}\pi_n(j,l)[1-\pi_n(j,l)]N_n(j,l)^2}, \tag{3.5}$$

$$\begin{aligned}\text{C3:}\quad \operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{M}^{-1}\right) = \sigma^2 \times \Bigg[&\sum_{j=1}^{J}\sum_{l=1}^{L}\frac{1}{N_n(j,l)\pi_n(j,l)[1-\pi_n(j,l)]}\\ &+\sum_{j=1}^{J}\frac{L+1}{N_n(j,0)\pi_n(j,0)[1-\pi_n(j,0)]}\\ &+\sum_{l=1}^{L}\frac{J+1}{N_n(0,l)\pi_n(0,l)[1-\pi_n(0,l)]}\\ &+\frac{(J+1)\times(L+1)}{N_n(0,0)\pi_n(0,0)[1-\pi_n(0,0)]}\Bigg].\end{aligned} \tag{3.6}$$

Furthermore, *criterion* C4 *coincides with* C5 *and is given by*

$$\begin{aligned}\operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D}\right) &= \operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{E}^t\mathbf{M}^{-1}\mathbf{E}\right)\\ &= \operatorname{tr}\left(\frac{\sigma^2}{n}\mathbf{M}^{-1}\right) - \frac{\sigma^2}{N_n(0,0)\pi_n(0,0)[1-\pi_n(0,0)]}.\end{aligned} \tag{3.7}$$

PROOF. See Appendix A.1. □

REMARK 3.1. Contrary to C1 and C2, from (3.6) and (3.7) it is easy to see that the trace criteria C3–C5 treat the covariate profiles in a different way due to the nature of the OLS estimators and the fact that these criteria correspond to the minimization of the mean variance of the estimators of the parameters of interest without taking into account their covariance structure.

Note that C1–C5 depend on the design only through the allocation vector $\boldsymbol{\pi}$; it is also straightforward to check that the above criteria are strictly convex in $\boldsymbol{\pi}$ and will be minimized by (3.2) independently on the covariates. However, the loss of inferential precision expressed by C1–C5 is random since it depends on the number of subjects within the different strata $\mathbf{N}_n$, that is, $\Phi_I = \Phi_I(\boldsymbol{\pi}_n, \mathbf{N}_n)$. Therefore, in order to remove the effect due to the random covariates, from now on we take into account the loss of inferential precision induced by the design

$$\widetilde{\Phi}_I(\boldsymbol{\pi}_n) = E_{\mathbf{Z}}[\Phi_I(\boldsymbol{\pi}_n, \mathbf{N}_n)]. \tag{3.8}$$

4. Optimal design for ethics. From an ethical viewpoint, a natural demand consists in an overall benefit for the entire sample of patients involved in the trial, for instance maximizing for any given sample size the percentage of patients who receive the best treatment. This make sense if and only if the treatment effects are different; otherwise there is no longer a worse treatment, stressing that the comparative experiment degenerates to just one treatment.

Assuming model (2.1), at each stratum (t_j, w_l) the superiority/inferiority of A or B depends only on the sign of θ in (2.2), and from now on we let for simplicity $\theta(j,l)$. Assuming "the-larger-the-better" scenario, for each subject with covariate profile (t_j, w_l) the allocation will be made to the superior treatment if $\delta_i \mathbb{1}_{\{\theta(j,l)>0\}} + (1-\delta_i)\mathbb{1}_{\{\theta(j,l)<0\}}$; otherwise, if $\theta(j,l)=0$ the two treatment arms collapse and all the allocations are equivalent (i.e., any ethical measurement is no longer useful). Thus, the percentage of patients assigned to the best treatment is

$$\frac{1}{n}\sum_{j=0}^{J}\sum_{l=0}^{L} N_n(j,l)\left\{\frac{1}{2} - \left[\frac{1}{2} - \pi_n(j,l)\right]\operatorname{sgn}(\theta(j,l))\right\},$$

where $\operatorname{sgn}(x)$ represents the sign of x. However, from (2.2) the relative performance of the treatments depends on the subject's covariates, so that a reasonable ethical measure is

$$\begin{aligned}(4.1)\qquad &\Phi_E(\boldsymbol{\pi}_n, \mathbf{N}_n)\\ &= \frac{1}{n}\sum_{j=0}^{J}\sum_{l=0}^{L} N_n(j,l)|\theta(j,l)|\left\{\frac{1}{2} - \left[\frac{1}{2} - \pi_n(j,l)\right]\operatorname{sgn}(\theta(j,l))\right\},\end{aligned}$$

under which every choice is weighed by the relative ethical gain $|\theta(j,l)|$. Obviously, criterion (4.1) depends on both the covariate profiles and the unknown parameters of the model and the optimal ethical target, namely the allocation that assigns all the patients to the better treatment, is

$$(4.2)\qquad \boldsymbol{\pi}_E^* = \left\{\pi_E^*(j,l) = \mathbb{1}_{\{\theta(j,l)>0\}} \text{ for any } j=0,\dots,J \text{ and } l=0,\dots,L\right\}.$$

REMARK 4.1. In the absence of treatment/covariate interactions, $\theta(j,l)=\alpha$ for any $j=0,\dots,J$ and $l=0,\dots,L$, so that criterion (4.1) simply becomes

$$\Phi_E(\boldsymbol{\pi}_n) = \frac{|\alpha|}{2} + \left(\frac{1}{n}\sum_{i=1}^{n}\delta_i - \frac{1}{2}\right)\alpha,$$

that depends on the design only through the total proportion of assignments to A. Thus, under (2.4) the percentage of allocations to the best treatment does not depend on the covariates, which are irrelevant from an ethical viewpoint, so that the optimal ethical target is $\pi_E^*(j,l) = \mathbb{1}_{\{\alpha>0\}}$ for any (j,l).

Analogously to (3.8), in order to remove the random effect due to covariates from now on we adopt as ethical criterion $\widetilde{\Phi}_E(\boldsymbol{\pi}_n) = E_{\mathbf{Z}}[\Phi_E(\boldsymbol{\pi}_n, \mathbf{N}_n)]$ given by

$$\widetilde{\Phi}_E(\boldsymbol{\pi}_n) = \sum_{j=0}^{J}\sum_{l=0}^{L} p(j,l)|\theta(j,l)|\left\{\frac{1}{2} - \left[\frac{1}{2} - \pi_n(j,l)\right]\operatorname{sgn}(\theta(j,l))\right\}. \tag{4.3}$$

5. The compromise criterion. In order to obtain a suitable compromise between inferential precision and ethical demands, there are several possible approaches. Among them, a trade-off the criteria via a combined or a constrained optimization has, to the best of our knowledge, the strongest theoretical justification; see, for example, [4, 9–11, 17, 22]. For the sake of generality, we now suggest a methodology based on the optimization of a compound criterion that mediates between information and ethics, since the constrained optimization approach can be regarded as a special case of this proposal (as it will be shown in Remark 6.1).

Note that, for any chosen inferential criterion C1–C5, $\widetilde{\Phi}_I$ and $\widetilde{\Phi}_E$ are not homogeneous measures, and in order to put them in a comparable scale, we consider their standardized version, that is,

$$\Psi_E(\boldsymbol{\pi}_n) = \frac{\widetilde{\Phi}_E(\boldsymbol{\pi}_n)}{\widetilde{\Phi}_E(\boldsymbol{\pi}_E^*)} \quad \text{and} \quad \Psi_I(\boldsymbol{\pi}_n) = \frac{\widetilde{\Phi}_I(\boldsymbol{\pi}_I^*)}{\widetilde{\Phi}_I(\boldsymbol{\pi}_n)}, \tag{5.1}$$

where $\boldsymbol{\pi}_I^*$ in (3.2) is the optimal inferential target minimizing $\widetilde{\Phi}^I$ and $\boldsymbol{\pi}_E^*$ in (4.2) maximizes (4.3) by assigning all subjects to the best treatment, with $\widetilde{\Phi}_E(\boldsymbol{\pi}_E^*) = E_{\mathbf{Z}}[|\theta(\mathbf{z})|] = \sum_{j=0}^{J}\sum_{l=0}^{L}|\theta(j,l)|p(j,l)$.

Clearly, $\Psi_E, \Psi_I : [0,1]^{(J+1)\cdot(L+1)} \to [0,1]$ represent standardized measures of ethical and inferential efficiency, respectively, that will be maximized. Therefore, by introducing an ethical weight ω, we let, as a compromise criterion,

$$\Psi_\omega(\boldsymbol{\pi}_n) = \omega\left\{\frac{1}{\Psi_E(\boldsymbol{\pi}_n)}\right\} + (1-\omega)\left\{\frac{1}{\Psi_I(\boldsymbol{\pi}_n)}\right\}, \tag{5.2}$$

which can be seen as the reciprocal of the weighted harmonic mean of Ψ_E and Ψ_I; see also [4, 11].

The ethical weight ω in the compound criterion can be chosen by the experimenter, with $0 \le \omega < 1$ (we assume $\omega \neq 1$ in order to avoid that the ethical impact completely overcomes the inferential goal). It may be fixed a priori or could be modeled as a function of the unknown parameters on the basis of the given real situation. In the latter case ω is allowed to depend on the true state of nature, since it is reasonable to suppose that the more the effects of the treatments differ, the more important for the patients are the chances of receiving the best treatment, whereas in the case of a small difference, which is more difficult to detect correctly, more emphasis is given on inferential precision. In particular, under (2.1) the ethical impact depends on the covariates, and thus, in order to express an overall measure of ethical risk for the population of interest, from now on we

let $\omega(E_{\mathbf{Z}}[|\theta(\mathbf{z})|]) : \mathbb{R}^+ \cup \{0\} \to [0; 1)$ to be a a continuous and increasing function with $\omega(0) \to 0$.

In general, the choice of the weight function depends on the given applied context. For instance, in Phase III trials the experimenters have often some information gathered from previous stage trials, and more attention is usually needed for inference, provided that the ethical costs are not prohibitive (such as deaths of patients). Thus, ω can be chosen to be an S-shaped function as

$$\omega_s(x) = (1 + x^{-2})^{-2(s+1)}[2 - (1 + x^{-2})^{-2}] \qquad \text{with } s \geq 0. \tag{5.3}$$

Additionally, since in several clinical situations it is reasonable to assume that the ethical concern is negligible in the case of small difference between the treatment performances, for example, up to a value ς of the overall risk, and then increases rapidly, we may assume $\omega(x) = 0$ for $x \leq \varsigma$, with $\omega(x) \to 0$ for $x \to \varsigma^+$, and $\omega(x) \to 1$ for $x \to \infty$. Whereas, an alternative choice for the ethical weight is the cdf of a chi-square r.v. $\chi^2_{(r)}$, where ω decreases as the degrees of freedom r increases. By fixing small degrees of freedom, the latter choice allows us to model the ethical impact in order to grow rapidly, even when the overall ethical risk is moderate.

THEOREM 5.1. *For every inferential criterion* C1–C5, *the compound criterion* $\Psi_\omega(\boldsymbol{\pi}_n)$ *is a strictly convex function of* $\boldsymbol{\pi}_n$, *so there exists a unique target allocation minimizing* (5.2) *which is the solution of the system of equations*

$$\begin{aligned}[\widetilde{\Phi}_E(\boldsymbol{\pi}_n)]^2 \frac{\partial \widetilde{\Phi}_I(\boldsymbol{\pi}_n)}{\partial \pi_n(j,l)} \\ = \left(\frac{\omega}{1-\omega}\right) \widetilde{\Phi}_E(\boldsymbol{\pi}_E^*) \widetilde{\Phi}_I(\boldsymbol{\pi}_I^*) \theta(j,l) p(j,l) \qquad \forall (j,l).\end{aligned} \tag{5.4}$$

PROOF. The suggested compound criterion is a linear combination of the reciprocals of Ψ_I and Ψ_E. Clearly, $[\Psi_I]^{-1}$ is strictly convex; moreover $\widetilde{\Phi}_E$ in (4.3) is linear, and thus concave, and it is also non-negative, so that Ψ_E is strictly convex in $\boldsymbol{\pi}_n$. Therefore, criterion (5.2) leads to a unique target allocation satisfying $\nabla \Psi_\omega(\boldsymbol{\pi}_n) = \mathbf{0}$, namely

$$\omega \widetilde{\Phi}_E(\boldsymbol{\pi}_E^*) \frac{\partial \{[\widetilde{\Phi}_E(\boldsymbol{\pi}_n)]^{-1}\}}{\partial \pi_n(j,l)} + \frac{1-\omega}{\widetilde{\Phi}_I(\boldsymbol{\pi}_I^*)} \left\{ \frac{\partial \widetilde{\Phi}_I(\boldsymbol{\pi}_n)}{\partial \pi_n(j,l)} \right\} = 0 \qquad \forall (j,l), \tag{5.5}$$

that leads to (5.4) after simple algebra. □

6. The optimal compound target. In this section we describe the properties of the allocation $\boldsymbol{\pi}_\omega^* = \{\pi_\omega^*(j,l) : j = 0, \ldots, J; l = 0, \ldots, L\}$ that minimizes the compromise criterion Ψ_ω in (5.2), and we shall refer to it as "optimal compound target." In general, $\boldsymbol{\pi}_\omega^*$ depends on the experimental choice of the inferential criterion $\widetilde{\Phi}_I$ and the ethical weight ω, as well as on the true state of the nature,

that is, the unknown parameters and the probability distribution $\mathbf{p} = \{p(j,l) : j = 0, \ldots, J; l = 0, \ldots, L\}$ of the covariates.

THEOREM 6.1. *For every chosen inferential criterion* C1–C5, *at each stratum* (t_j, w_l) *the optimal compound target* $\pi^*_\omega(j,l)$ *satisfies the following properties*:

- $\pi^*_\omega(j,l) \in (0,1)$ *is a continuous function of* α, $\boldsymbol{\tau}$ *and* $\mathbf{p}$, *that is*, $\pi^*_\omega(j,l) = \pi^*_\omega(j,l;\alpha,\boldsymbol{\tau},\mathbf{p})$, *and it is increasing in* $\theta(j,l)$;
- *if* $(\alpha', \boldsymbol{\tau}')$ *and* $(\alpha'', \boldsymbol{\tau}'')$ *are parameter values with corresponding ethical gains* $\theta'(j,l) = -\theta''(j,l)$, *then for any given covariate distribution* $\mathbf{p}$,

$$\pi^*_\omega(j,l;\alpha',\boldsymbol{\tau}',\mathbf{p}) = 1 - \pi^*_\omega(j,l;\alpha'',\boldsymbol{\tau}'',\mathbf{p}), \tag{6.1}$$

  so that the optimal compound target always assigns more than half the subjects to the better treatment;
- *if* $\theta(j,l) > 0$, *then* $\pi^*_\omega(j,l)$ *is increasing in* $p(j,l)$, *whereas when* $\theta(j,l) < 0$, *then* $\pi^*_\omega(j,l)$ *is decreasing in* $p(j,l)$.

PROOF. For any given stratum (t_j, w_l), let $k(\pi_n(j,l)) = \partial\widetilde{\Phi}_I(\boldsymbol{\pi}_n)/\partial\pi_n(j,l)$. From the convexity of the inferential criterion, the function $k(\cdot)$ is monotonically increasing with $k(1/2) = 0$, due to the optimality of the jointly balanced design in (3.2). Furthermore, the right-hand side of (5.4) is a continuous function of α, $\boldsymbol{\tau}$ and $\mathbf{p}$, due to the properties of $\omega(\cdot)$; it is straightforward to check that, for any given $p(j,l)$, it is also an increasing function of $\theta(j,l)$ and is monotone in $p(j,l)$ (increasing when $\theta(j,l) > 0$ and decreasing if $\theta(j,l) < 0$). Since the sign of the left-hand side of (5.4) depends only on the sign of $k(\cdot)$, if $\theta(j,l) > 0$ (i.e., A is better than B for this stratum), then the right-hand side of (5.4) is positive and thus the optimal compound target $\pi^*_\omega(j,l) > 1/2$; otherwise, if $\theta(j,l) < 0$, then $\pi^*_\omega(j,l) < 1/2$ and $\theta(j,l) = 0$ if and only if $\pi^*_\omega(j,l) = 1/2$. Moreover, observe that $\lim_{\zeta\to 0} k(\zeta) = -\infty$ and $\lim_{\zeta\to 1} k(\zeta) = +\infty$ and thus $\pi^*_\omega(j,l) \neq \{0,1\}$, since $\widetilde{\Phi}_E(\cdot)$ is limited. By taking the derivative of the left-hand side of (5.4) with respect to $\pi_n(j,l)$ we obtain

$$\frac{\partial k(\pi_n(j,l))}{\partial \pi_n(j,l)}[\widetilde{\Phi}_E(\boldsymbol{\pi}_n)]^2 + 2\widetilde{\Phi}_E(\boldsymbol{\pi}_n)k(\pi_n(j,l))\theta(j,l)p(j,l),$$

where the first term is always positive, due to the convexity of the inferential criterion. Furthermore, locally around $\pi^*_\omega(j,l)$

$$k(\pi^*_\omega(j,l))\theta(j,l)p(j,l) > 0,$$

since if $\theta(j,l) > 0$, then $\pi^*_\omega(j,l) > 1/2$ and $k(\pi^*_\omega(j,l)) > 0$ (and, analogously, when $\theta(j,l) < 0$). Thus, as a function of $\pi_n(j,l)$ the left-hand side of (5.4) is locally increasing around $\pi^*_\omega(j,l)$, so that $\pi^*_\omega(j,l)$ is a continuous function of α,

$\boldsymbol{\tau}$ and $\mathbf{p}$ and it is increasing in $\theta(j,l)$ and $p(j,l)$, due to the property of the right-hand side of (5.4). Concerning (6.1), for a given covariate distribution $\mathbf{p}$ the ethical criterion in (4.3) can be regarded as a function of $\pi_n(j,l)$ and $\theta(j,l)$ by letting

$$\sum_{j=0}^{J}\sum_{l=0}^{L}|\theta(j,l)|p(j,l)\left\{\frac{1}{2}-\left[\frac{1}{2}-\pi_n(j,l)\right]\operatorname{sgn}(\theta(j,l))\right\}=\upsilon+g(\pi_n(j,l),\theta(j,l)),$$

where

$$g(\pi_n(j,l),\theta(j,l))=|\theta(j,l)|p(j,l)\left\{\frac{1}{2}-\left[\frac{1}{2}-\pi_n(j,l)\right]\operatorname{sgn}(\theta(j,l))\right\},$$

so the left-hand side of (5.4) can be rewritten as $[\upsilon + g(\pi_n(j,l),\theta(j,l))]\cdot k(\pi_n(j,l))$. First of all note that, for every chosen inferential criterion C1–C5 the function $k(\cdot)$ is symmetric around the point $(1/2;0)$ since $k(1/2+\epsilon)=-k(1/2-\epsilon)$ for any $\epsilon\in(0;1/2)$. Moreover, $g(1/2+\epsilon,\theta(j,l))=g(1/2-\epsilon,-\theta(j,l))$, so that the left-hand side of (5.4) is also symmetric around $(1/2;0)$, and this implies the symmetric property of the compound target. □

6.1. *Example*: *the inferential criteria based on the determinant*. From (3.4) and (3.5) it is easy to see that C1 and C2 have the same standardized version,

$$\Psi_I(\boldsymbol{\pi}_n)=4^{(J+1)(L+1)}\prod_{j=0}^{J}\prod_{l=0}^{L}\pi_n(j,l)[1-\pi_n(j,l)]. \tag{6.2}$$

Assuming now two binary covariates and two different scenarios for their population distribution, that is, a uniform one $\mathcal{U}$ where each stratum is equally represented, that is, $p(0,0)=p(1,0)=p(0,1)=p(1,1)=0.25$, and a nonuniform distribution $\mathcal{NU}$ with $p(0,0)=0.2$, $p(1,0)=0.3$, $p(0,1)=0.4$, $p(1,1)=0.1$. Table 1 shows the derived optimal compound targets in the case of four different ethical weights, namely the cdf's of a $\chi^2_{(r)}$ with $r=1,2$ and ω_s in (5.3) with $s=1,2$.

The optimal compound target always assigns the majority of subjects to the better treatment. The ethical weight increases as r and s decrease, and therefore less emphasis is given to the inferential precision and more attention to ethical demands, as expected. Furthermore, since criteria C1 and C2 treat every stratum in the same way, when $p(j,l)=p(\widetilde{j},\widetilde{l})$ and $\theta(j,l)=1-\theta(\widetilde{j},\widetilde{l})$, then $\pi^*_\omega(j,l)=1-\pi^*_\omega(\widetilde{j},\widetilde{l})$.

6.2. *Example*: *the inferential criteria based on the trace*. Consider two binary covariates under the same settings of the previous example. By taking the approximation $E_{\mathbf{Z}}[N_n(j,l)^{-1}]=[np(j,l)]^{-1}$, Table 2 shows the optimal compound targets when the inferential criterion C3 is adopted, whereas Table 3 deals with criterion C4 (or, equivalently, C5).

TABLE 1
Optimal compound targets adopting criteria C1–C2

		$(\alpha, \tau^t) = (1, 1, 1, 1)$				$(\alpha, \tau^t) = (-4, -1, 3, 3)$			
		$\theta(0,0) = 1$ $\pi^*_\omega(0,0)$	$\theta(1,0) = 2$ $\pi^*_\omega(1,0)$	$\theta(0,1) = 2$ $\pi^*_\omega(0,1)$	$\theta(1,1) = 4$ $\pi^*_\omega(1,1)$	$\theta(0,0) = -4$ $\pi^*_\omega(0,0)$	$\theta(1,0) = -5$ $\pi^*_\omega(1,0)$	$\theta(0,1) = -1$ $\pi^*_\omega(0,1)$	$\theta(1,1) = 1$ $\pi^*_\omega(1,1)$
$\chi^2_{(1)}$	$\mathcal{NU}$	0.578	0.700	0.743	0.646	0.278	0.186	0.371	0.534
	$\mathcal{U}$	0.593	0.670	0.670	0.771	0.242	0.209	0.415	0.585
$\chi^2_{(2)}$	$\mathcal{NU}$	0.544	0.623	0.660	0.587	0.352	0.264	0.421	0.520
	$\mathcal{U}$	0.554	0.605	0.605	0.689	0.319	0.287	0.449	0.551
ω_1	$\mathcal{NU}$	0.537	0.606	0.637	0.572	0.353	0.265	0.421	0.520
	$\mathcal{U}$	0.549	0.596	0.596	0.674	0.321	0.289	0.449	0.551
ω_2	$\mathcal{NU}$	0.521	0.562	0.581	0.541	0.397	0.324	0.447	0.513
	$\mathcal{U}$	0.530	0.559	0.559	0.614	0.373	0.346	0.466	0.534

TABLE 2
Optimal compound targets adopting criterion C3

		$(\alpha, \tau^t) = (1, 1, 1, 1)$				$(\alpha, \tau^t) = (-4, -1, 3, 3)$			
		$\theta(0,0) = 1$ $\pi^*_\omega(0,0)$	$\theta(1,0) = 2$ $\pi^*_\omega(1,0)$	$\theta(0,1) = 2$ $\pi^*_\omega(0,1)$	$\theta(1,1) = 4$ $\pi^*_\omega(1,1)$	$\theta(0,0) = -4$ $\pi^*_\omega(0,0)$	$\theta(1,0) = -5$ $\pi^*_\omega(1,0)$	$\theta(0,1) = -1$ $\pi^*_\omega(0,1)$	$\theta(1,1) = 1$ $\pi^*_\omega(1,1)$
$\chi^2_{(1)}$	$\mathcal{NU}$	0.658	0.868	0.900	0.805	0.179	0.077	0.128	0.677
	$\mathcal{U}$	0.697	0.835	0.835	0.916	0.154	0.099	0.214	0.846
$\chi^2_{(2)}$	$\mathcal{NU}$	0.572	0.792	0.841	0.706	0.277	0.125	0.205	0.582
	$\mathcal{U}$	0.598	0.745	0.745	0.866	0.241	0.158	0.318	0.759
ω_1	$\mathcal{NU}$	0.557	0.767	0.821	0.678	0.279	0.126	0.206	0.581
	$\mathcal{U}$	0.586	0.728	0.728	0.856	0.243	0.159	0.320	0.757
ω_2	$\mathcal{NU}$	0.530	0.696	0.760	0.610	0.346	0.169	0.268	0.546
	$\mathcal{U}$	0.548	0.658	0.658	0.806	0.308	0.210	0.382	0.692

TABLE 3
Optimal compound targets adopting criteria C4 *or* C5

		$(\alpha, \tau^t) = (1, 1, 1, 1)$				$(\alpha, \tau^t) = (-4, -1, 3, 3)$			
		$\theta(0,0) = 1$ $\pi^*_\omega(0,0)$	$\theta(1,0) = 2$ $\pi^*_\omega(1,0)$	$\theta(0,1) = 2$ $\pi^*_\omega(0,1)$	$\theta(1,1) = 4$ $\pi^*_\omega(1,1)$	$\theta(0,0) = -4$ $\pi^*_\omega(0,0)$	$\theta(1,0) = -5$ $\pi^*_\omega(1,0)$	$\theta(0,1) = -1$ $\pi^*_\omega(0,1)$	$\theta(1,1) = 1$ $\pi^*_\omega(1,1)$
$\chi^2_{(1)}$	$\mathcal{NU}$	0.677	0.860	0.895	0.795	0.166	0.082	0.137	0.663
	$\mathcal{U}$	0.717	0.827	0.827	0.912	0.142	0.105	0.225	0.837
$\chi^2_{(2)}$	$\mathcal{NU}$	0.585	0.782	0.833	0.694	0.259	0.133	0.217	0.573
	$\mathcal{U}$	0.615	0.734	0.734	0.859	0.223	0.167	0.331	0.747
ω_1	$\mathcal{NU}$	0.567	0.756	0.812	0.666	0.261	0.134	0.218	0.572
	$\mathcal{U}$	0.601	0.717	0.717	0.849	0.225	0.169	0.333	0.744
ω_2	$\mathcal{NU}$	0.536	0.685	0.749	0.601	0.328	0.179	0.282	0.541
	$\mathcal{U}$	0.558	0.645	0.645	0.797	0.289	0.221	0.393	0.679

Note that, since C3–C5 treat the strata in a different way, even if $p(0,1) = p(1,1) = 0.25$ and $\theta(0,1) = -\theta(1,1) = -1$, that is, when $(\alpha, \boldsymbol{\tau}^t) = (-4, -1, 3, 3)$, then $\pi^*_\omega(0,1) \neq 1 - \pi^*_\omega(1,1)$.

In general, when $r = s$ the ethical skew is larger if we adopt the cdf of $\chi^2_{(r)}$ w.r.t. ω_s, and this skew is particularly high for $r = 1$, which could induce strong imbalances among the treatment groups (see Tables 1–3 with $(\alpha, \boldsymbol{\tau}^t) = (-4, -1, 3, 3)$) and, consequently, a great loss of inferential efficiency. This behavior suggests that the adoption of the cdf of $\chi^2_{(1)}$ is adequate only in situations with prohibitive ethical costs.

REMARK 6.1. Using the analytical expressions of the inferential criteria given in Proposition 3.1, by (5.1) it is also possible to derive optimal targets via a constrained optimization approach. In the same spirit of [22], the problem lies in finding the allocation that maximizes the ethical impact for a chosen inferential efficiency. In our context this corresponds to minimize Ψ_E^{-1} under the constraint $\Psi_I^{-1} \leq C^{-1}$ for a prefixed constant $C < 1$ (we exclude the degenerate case $C = 1$ that corresponds to assume $\Psi_I = 1$, i.e., no ethical concerns), representing a special case of our combined optimization approach; see also [4, 9, 10]. Indeed, due to the strict convexity of both Ψ_E^{-1} and Ψ_I^{-1}, this is a convex optimization problem, and therefore the Karush–Kuhn–Tucker (KKT) first order conditions are necessary and sufficient and guarantee a unique optimal solution $\boldsymbol{\pi}^*$ solving

$$\nabla(\Psi_E^{-1}(\boldsymbol{\pi}^*)) + \kappa \nabla(\Psi_I^{-1}(\boldsymbol{\pi}^*)) = \mathbf{0}, \tag{6.3}$$

where $\kappa \geq 0$ is the KKT multiplier and

$$\kappa\big(\Psi_I^{-1}(\boldsymbol{\pi}^*) - C^{-1}\big) = 0. \tag{6.4}$$

First, note that (6.3) corresponds to (5.4) with $\kappa = (1-\omega)/\omega$ (where clearly $\omega \neq 0$, since $C \neq 1$); thus, the candidate solution $\boldsymbol{\pi}^*$ belongs to the class of compound optimal targets and should satisfy $\Psi_I^{-1}(\boldsymbol{\pi}^*) = C^{-1}$, since $\kappa > 0$. By using the same arguments of the proof of Theorem 6.1, any compound target $\boldsymbol{\pi}^*_\omega$ solving (5.4) is a continuous and monotone function of ω and, from the properties of Ψ_I^{-1}, for any fixed $C < 1$ there exists a unique constant weight $\omega = \omega_C$ such that $\boldsymbol{\pi}^* = \boldsymbol{\pi}^*_{\omega_C}$ satisfies (6.4).

As a numerical example, consider now the standardized inferential criterion (6.2) in the case of two binary covariates with $(\alpha, \boldsymbol{\tau}^t) = (1, 1, 1, 1)$ and uniform distribution $\mathcal{U}$. The upper block of Table 4 shows the derived constrained optimal targets as C varies, together with the corresponding ethical weight ω_C of our combined optimization approach and the value of the ethical criterion Ψ_E. Moreover, the bottom part of the Table gives the asymptotic allocations of the procedure suggested by Bandyopadhyay and Biswas [7] (and further analyzed in [3]), which are given at each stratum (j, l) by the standard normal cdf evaluated at $\theta(j,l)/T$, for $T = 1, 2$ and 3. For instance, an inferential efficiency equal to 75% under the con-

TABLE 4
Constrained optimal targets adopting criteria C1–C2 *and Bandyopadhyay and Biswas's allocations* π_T, *with* $(\alpha, \boldsymbol{\tau}^t) = (1, 1, 1, 1)$ *and uniform distribution*

	$\boldsymbol{\theta(0,0)=1}$	$\boldsymbol{\theta(1,0)=2}$	$\boldsymbol{\theta(0,1)=2}$	$\boldsymbol{\theta(1,1)=4}$	$\boldsymbol{\Psi_E}$	$\boldsymbol{\Psi_I = C}$
	$\pi^*_{\omega_C}(0,0)$	$\pi^*_{\omega_C}(1,0)$	$\pi^*_{\omega_C}(0,1)$	$\pi^*_{\omega_C}(1,1)$		
$\omega_C = 0.356$	0.523	0.546	0.546	0.589	0.56	0.95
$\omega_C = 0.483$	0.528	0.566	0.566	0.612	0.59	0.9
$\omega_C = 0.700$	0.558	0.612	0.612	0.698	0.64	0.75
$\omega_C = 0.883$	0.599	0.679	0.679	0.781	0.72	0.5
$\omega_C = 0.969$	0.656	0.756	0.756	0.851	0.79	0.25
	$\pi_T(0,0)$	$\pi_T(1,0)$	$\pi_T(0,1)$	$\pi_T(1,1)$		
$T = 1$	0.841	0.977	0.977	0.999	0.97	10^{-6}
$T = 2$	0.691	0.841	0.841	0.977	0.88	0.02
$T = 3$	0.631	0.748	0.748	0.909	0.81	0.17

strained approach corresponds to an ethical weight equal to 70% in the combined framework; whereas, assuming $C = 0.25$ means that the role of ethics is almost dominant in the combined optimization. Clearly, the arbitrary choice of the constant C in the constrained setting can be directly translated in the subjective choice of ω in the combined approach; however, the possibility of modeling the ethical weight as a function of the unknown parameters allows us to discriminate among different situations that could be a-priori only partially known or, more commonly, completely unknown. For instance, if we set $\omega_C = 0.483$, then the 38.8% of subjects within the stratum $(1, 1)$ will receive the worst treatment; whereas, the percentage of allocations to the worst treatment is only 22.9% or 32,6% if the cdf of $\chi^2_{(1)}$ or ω_1 are assumed as weight functions, respectively; see Table 1. Moreover, the allocations proposed by Bandyopadhyay and Biswas (2001) are strongly skewed toward the better treatment, so that the inferential precision collapses. This is particularly true for small values of T, as emphasized in [18], and this behavior is also confirmed, even if we adopt criteria C3–C5.

7. The reinforced doubly adaptive biased coin design. As shown previously, the compound target allocation $\boldsymbol{\pi}^*_\omega$ depends in general on the unknown parameters of the model and, since this function is continuous, covariate-adjusted response-adaptive procedures may be called for. These designs use at each step the observed responses, the covariates and the previous assignments, as well as the covariate profile of the current subject, to modify the allocations as the experiment goes along in order to gradually approach the desired target.

In this section we introduce the reinforced doubly adaptive biased coin design. This is a general class of CARA procedures, which admits both continuous and discontinuous randomization functions, aimed at targeting any chosen allocation proportion by forcing closeness to the target when necessary.

Let now $\boldsymbol{\pi}^* = \{\pi^*(j,l) : j = 0, \ldots, J; l = 0, \ldots, L\}$ be a desired allocation such that, at each stratum (t_j, w_l), $\pi^*(j,l) \in (0,1)$ is a continuous function of the unknown model parameters $\boldsymbol{\gamma}$ and $\mathbf{p}$. Suppose that patients come to the trial sequentially and are assigned to either treatment. Starting with m observations on each treatment, usually assigned by using restricted randomization, an initial non-trivial parameter estimation $\widehat{\boldsymbol{\gamma}}_{2m}$ and $\widehat{\mathbf{p}}_{2m}$ is derived. Then, at each step n ($n > 2m$) let $\widehat{\boldsymbol{\gamma}}_n$ and $\widehat{\mathbf{p}}_n$ be the estimators of the parameters based on the first n observations, where we assume them consistent in case of i.i.d. observations, so that the optimal target will be estimated by all the data up to that step by $\widehat{\boldsymbol{\pi}}_n^* = \boldsymbol{\pi}^*(\widehat{\boldsymbol{\gamma}}_n, \widehat{\mathbf{p}}_n)$. When the $(n+1)$st patient with covariate profile $Z_{n+1} = (t_j, w_l)$ is ready to be randomized, the reinforced doubly adaptive biased coin design assigns to him/her treatment A with probability

$$\varphi(\pi_n(j,l); \widehat{\pi}_n^*(j,l); \widehat{p}_n(j,l)), \tag{7.1}$$

where the function $\varphi(x,y,z) : (0,1)^3 \to [0,1]$ satisfies the following properties:

(i) φ is decreasing in x and increasing in y, for any $z \in (0,1)$;
(ii) $\varphi(x,x,z) = x$ for any $z \in (0,1)$;
(iii) φ is decreasing in z if $x < y$, and increasing in z if $x > y$;
(iv) $\varphi(x,y,z) = 1 - \varphi(1-x, 1-y, z)$ for any $z \in (0,1)$.

Adopting the RDBCD in (7.1), within each stratum the allocation proportion will be forced to the corresponding target, since from conditions (i)–(ii) when $x \geq y$, then $\varphi(x,y,z) \leq y$ and if $x < y$, then $\varphi(x,y,z) > y$ for any $z \in (0,1)$. Furthermore, condition (iv) simply guarantees that A and B are treated symmetrically, whereas (iii) means that the allocation is forced towards optimality increasingly as the representativeness of the strata in the population decreases. This property is of great importance since the convergence of the allocation proportion depends on the number of subjects belonging to each stratum, and therefore it is related to the population distribution of the covariates. This may be particularly critical for small samples, where some profiles could be strongly under-represented so that, both from the ethical and inferential viewpoint, the need to force the closeness to the target could be greater.

REMARK 7.1. In general, at each step the allocation probability (7.1) does not depend only on the estimates of the unknown parameters related to the stratum where the current subject belongs; in fact, $\widehat{\pi}_n^*(j,l)$ could involve the estimation of the entire set of parameters $\boldsymbol{\gamma}$ and $\mathbf{p}$. For example, if we adopt the optimal compound target $\boldsymbol{\pi}_\omega^*$, at each stratum $\pi_\omega^*(j,l)$ depends on α, $\boldsymbol{\tau}$ and $\mathbf{p}$ [see, for instance, (5.4)], so that (7.1) depends on the information gathered up to that step from all the strata.

Observe that we do not assume the continuity of φ, and therefore it is possible to consider discontinuous randomization functions. For instance, a natural extension

of the ERADE proposed by [14] in the presence of covariates is

$$\varphi_{\mathrm{ERADE}}(x;y;z)=\begin{cases}1-\rho(1-y), & x<y,\\ y, & x=y,\\ \rho y, & x>y\end{cases}\qquad \forall z\in(0,1), \tag{7.2}$$

where the constant $\rho\in[0,1)$ controls the degree of randomness.

REMARK 7.2. The randomization function in (7.1) could also be chosen in a different way for each stratum (t_j,w_l) by letting $\varphi=\varphi_{jl}$, in order to discriminate the importance of each of them and the corresponding closeness to the target. Furthermore, the RDBCD can be naturally extended to the case of several treatments.

An interesting family of allocation functions belonging to the RDBCD is

$$\begin{aligned}\varphi(x;y;z)&=F\big[D(x;y)^{H(z)}F^{-1}(y)\big]\\ &\quad/\big(F\big[D(x;y)^{H(z)}F^{-1}(y)\big]\\ &\qquad+F\big[D(1-x;1-y)^{H(z)}F^{-1}(1-y)\big]\big),\end{aligned} \tag{7.3}$$

where $F:\mathbb{R}^+\to\mathbb{R}^+$ is continuous and strictly increasing, $H(z)$ is decreasing, while $D(x;y):(0;1)^2\to\mathbb{R}^+$ represents a dissimilarity measure between the actual allocation proportion x and the current estimate of the optimal target y, and D is assumed to be decreasing in x and increasing in y, with $D(x;x)=1$.

EXAMPLE 7.1. Letting $D(x;y)=1$ for any $(x,y)\in(0,1)^2$, then (7.3) corresponds to the CARA design analyzed by Zhang et al. [23], namely

$$\varphi_Z(x;y;z)=y\qquad\forall(x,z)\in(0,1)^2, \tag{7.4}$$

which represents an analog of the sequential maximum likelihood design in the presence of covariates. Whereas if we let $F(t)=t$, $D(x;y)=y/x$ and $H(z)=\nu\geq 0\ \forall z\in(0,1)$, we obtain a natural extension in the presence of covariates of the family of doubly adaptive biased coin designs, that is,

$$\frac{y(y/x)^{\nu}}{y(y/x)^{\nu}+(1-y)[(1-y)/(1-x)]^{\nu}}\qquad\forall z\in(0,1).$$

However, note that the previous allocation function does not correspond to the covariate-adjusted doubly adaptive biased coin design suggested by Zhang and Hu in [24], due to the fact that these authors assume at each step n a dissimilarity measure between the actual allocation proportion $\pi_n(j,l)$ and the mean (over the steps) of the estimates of the optimal target $n^{-1}\sum_{i=1}^n\widehat{\pi}_i^*(j,l)$, instead of the current estimate of the target $\widehat{\pi}_n^*(j,l)$ itself.

EXAMPLE 7.2. If we set $F(t) = t^k$ with $k > 0$, $D(x; y) = 1 - (x - y)$ and $H(z) = z^{-1}$ $\forall z \in (0, 1)$, then (7.3) becomes

$$\varphi_{BAZ_1}(x; y; z) = \frac{y[1 - (x - y)]^{k/z}}{y[1 - (x - y)]^{k/z} + (1 - y)[1 - (y - x)]^{k/z}}. \tag{7.5}$$

In order to account for discontinuous allocation functions, let for instance $F(t) = t$, $H(z) = \{(J + 1)(L + 1)z\}^{-1}$ and

$$D(x; y) = \begin{cases} 1 + \varepsilon, & x < y, \\ 1, & x = y, \\ 1 - \varepsilon, & x > y, \end{cases}$$

with $\varepsilon \in [0, 1)$. Then (7.3) becomes

$$\varphi_{BAZ_2}(x; y; z) = \begin{cases} \dfrac{y(1+\varepsilon)^{\{(J+1)(L+1)z\}^{-1}}}{y(1+\varepsilon)^{\{(J+1)(L+1)z\}^{-1}} + (1-y)(1-\varepsilon)^{\{(J+1)(L+1)z\}^{-1}}}, \\ \qquad x < y, \\ y, \qquad x = y, \\ \dfrac{y(1-\varepsilon)^{\{(J+1)(L+1)z\}^{-1}}}{y(1-\varepsilon)^{\{(J+1)(L+1)z\}^{-1}} + (1-y)(1+\varepsilon)^{\{(J+1)(L+1)z\}^{-1}}}, \\ \qquad x > y, \end{cases} \tag{7.6}$$

which allows us to force the allocations toward the chosen target increasingly the more we move away from the uniform distribution, maintaining at the same time a good degree of randomness.

REMARK 7.3. If we assume only an inferential viewpoint by letting $\omega = 0$, then the optimal target is the jointly balanced allocation in (3.2), so that the allocation probability (7.1) corresponds to a stratified randomization. For instance, letting $F(t) = t^2$, $H(z) = 1$ and $D(x; y = 1/2) = 1 - 2(x - 1/2)$, then procedure (7.3) corresponds to the D_A-optimal design proposed by Atkinson [1],

$$\frac{[1 - \pi_n(j, l)]^2}{[1 - \pi_n(j, l)]^2 + \pi_n(j, l)^2};$$

see the supplementary data in [5] for details.

Let $\boldsymbol{\pi}^*_{t_j \otimes \mathbb{W}} = (\pi^*(j, 1)p(j, 1), \ldots, \pi^*(j, L)p(j, L))^t$ and $\widetilde{\boldsymbol{\pi}}^{*t} = (\boldsymbol{\pi}^{*t}_{\mathbb{T}}, \boldsymbol{\pi}^{*t}_{\mathbb{W}}, \boldsymbol{\pi}^{*t}_{\mathbb{T} \otimes \mathbb{W}})$, where

$$\boldsymbol{\pi}^*_{\mathbb{T}} = \left(\sum_{l=0}^{L} \pi^*(1, l)p(1, l), \ldots, \sum_{l=0}^{L} \pi^*(J, l)p(J, l) \right)^t,$$

$$\boldsymbol{\pi}^*_{\mathbb{W}} = \left(\sum_{j=0}^{J} \pi^*(j, 1)p(j, 1), \ldots, \sum_{j=0}^{J} \pi^*(j, L)p(j, L) \right)^t$$

and $\boldsymbol{\pi}^*_{\mathbb{T}\otimes\mathbb{W}}$ given by

$$(\pi^*(1,1)p(1,1),\dots,\pi^*(1,L)p(1,L),\dots,$$
$$\pi^*(J,1)p(J,1),\dots,\pi^*(J,L)p(J,L))^t.$$

The following theorem establishes the strong consistency of both the allocation proportion and the estimator of the target, as well as the strong consistency and asymptotic normality of the estimators of the unknown parameters of the model.

THEOREM 7.1. *For any given target allocation* $\boldsymbol{\pi}^* \in (0,1)^{(J+1)\cdot(L+1)}$ *which is a continuous function of the unknown model parameters* $\boldsymbol{\gamma}$ *and* $\mathbf{p}$, *then adopting the reinforced doubly adaptive biased coin design* (7.1), *as* n *tends to infinity*

$$\boldsymbol{\pi}_n \to \boldsymbol{\pi}^* \quad a.s. \quad \text{and} \quad \widehat{\boldsymbol{\pi}}^*_n \to \boldsymbol{\pi}^* \quad a.s. \tag{7.7}$$

Furthermore,

$$\hat{\boldsymbol{\gamma}}_n \to \boldsymbol{\gamma} \quad a.s. \quad \text{and} \quad \sqrt{n}(\hat{\boldsymbol{\gamma}}_n - \boldsymbol{\gamma}) \to N(\mathbf{0}; \boldsymbol{\mathcal{M}}^{-1}(\boldsymbol{\pi}^*)) \quad \text{in law}, \tag{7.8}$$

where $\boldsymbol{\mathcal{M}}(\boldsymbol{\pi}^*)$ *is*

$$\left(\begin{array}{cc|cc} \displaystyle\sum_{j=0}^{J}\sum_{l=0}^{L}\pi^*(j,l)p(j,l) & 0 & \widetilde{\boldsymbol{\pi}}^{*t} & \mathbf{0}_{1\times p} \\ 0 & \displaystyle 1-\sum_{j=0}^{J}\sum_{l=0}^{L}\pi^*(j,l)p(j,l) & \mathbf{0}_{1\times p} & \mathbf{1}^t_p - \widetilde{\boldsymbol{\pi}}^{*t} \\ \hline \widetilde{\boldsymbol{\pi}}^* & \mathbf{0}_{p\times 1} & \boldsymbol{\mathcal{M}}^A & \mathbf{0}_{p\times p} \\ \mathbf{0}_{p\times 1} & \mathbf{1}_p - \widetilde{\boldsymbol{\pi}}^* & \mathbf{0}_{p\times p} & \boldsymbol{\mathcal{M}}^B \end{array}\right),$$

with

$$\boldsymbol{\mathcal{M}}^A = \left(\begin{array}{c|c} \boldsymbol{\mathcal{M}}^A_{11} & \boldsymbol{\mathcal{M}}^A_{12} \\ \hline (\boldsymbol{\mathcal{M}}^A_{12})^t & \boldsymbol{\mathcal{M}}^A_{22} \end{array}\right), \tag{7.9}$$

such that $\boldsymbol{\mathcal{M}}^A_{22} = \operatorname{diag}(\boldsymbol{\pi}^*_{\mathbb{T}\otimes\mathbb{W}})$,

$$\boldsymbol{\mathcal{M}}^A_{11} = \left(\begin{array}{ccc|c} & \operatorname{diag}(\boldsymbol{\pi}^*_{\mathbb{T}}) & & \boldsymbol{\pi}^{*t}_{t_1\otimes\mathbb{W}} \\ & & & \vdots \\ & & & \boldsymbol{\pi}^{*t}_{t_J\otimes\mathbb{W}} \\ \hline \boldsymbol{\pi}^*_{t_1\otimes\mathbb{W}} & \dots & \boldsymbol{\pi}^*_{t_J\otimes\mathbb{W}} & \operatorname{diag}(\boldsymbol{\pi}^*_{\mathbb{W}}) \end{array}\right),$$

$$\boldsymbol{\mathcal{M}}^A_{12} = \left(\begin{array}{cccc} \boldsymbol{\pi}^{*t}_{t_1\otimes\mathbb{W}} & \mathbf{0} & \mathbf{0} & \dots & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\pi}^{*t}_{t_2\otimes\mathbb{W}} & \mathbf{0} & \dots & \mathbf{0} \\ \vdots & & \ddots & & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \dots & & \boldsymbol{\pi}^{*t}_{t_J\otimes\mathbb{W}} \\ \hline \operatorname{diag}(\boldsymbol{\pi}^*_{t_1\otimes\mathbb{W}}) & \operatorname{diag}(\boldsymbol{\pi}^*_{t_2\otimes\mathbb{W}}) & \dots & & \operatorname{diag}(\boldsymbol{\pi}^*_{t_J\otimes\mathbb{W}}) \end{array}\right).$$

Moreover, $\mathcal{M}^B$ *is partitioned similarly to* (7.9) *with treatment* A *replaced by* B, *that is,* $\mathcal{M}^B_{22} = \operatorname{diag}(\mathbf{1}_{JL} - \boldsymbol{\pi}^*_{\mathbb{T}\otimes\mathbb{W}})$,

$$\mathcal{M}^B_{11} = \left(\begin{array}{ccc|c} & \operatorname{diag}(\mathbf{1}_J - \boldsymbol{\pi}^*_{\mathbb{T}}) & & \begin{matrix}\mathbf{1}^t_L - \boldsymbol{\pi}^{*t}_{t_1\otimes\mathbb{W}} \\ \vdots \\ \mathbf{1}^t_L - \boldsymbol{\pi}^{*t}_{t_J\otimes\mathbb{W}}\end{matrix} \\ \hline \mathbf{1}_L - \boldsymbol{\pi}^*_{t_1\otimes\mathbb{W}} & \dots & \mathbf{1}_L - \boldsymbol{\pi}^*_{t_J\otimes\mathbb{W}} & \operatorname{diag}(\mathbf{1}_L - \boldsymbol{\pi}^*_{\mathbb{W}}) \end{array}\right),$$

$$\mathcal{M}^B_{12} = \left(\begin{array}{cccc} \mathbf{1}^t_L - \boldsymbol{\pi}^{*t}_{t_1\otimes\mathbb{W}} & \mathbf{0} & \mathbf{0} & \dots & \mathbf{0} \\ \mathbf{0} & \mathbf{1}^t_L - \boldsymbol{\pi}^{*t}_{t_2\otimes\mathbb{W}} & \mathbf{0} & \dots & \mathbf{0} \\ \vdots & & \ddots & & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \dots & & \mathbf{1}^t_L - \boldsymbol{\pi}^{*t}_{t_J\otimes\mathbb{W}} \\ \hline \operatorname{diag}(\mathbf{1}_L - \boldsymbol{\pi}^*_{t_1\otimes\mathbb{W}}) & \operatorname{diag}(\mathbf{1}_L - \boldsymbol{\pi}^*_{t_2\otimes\mathbb{W}}) & \dots & & \operatorname{diag}(\mathbf{1}_L - \boldsymbol{\pi}^*_{t_J\otimes\mathbb{W}}) \end{array}\right).$$

PROOF. See Appendix A.2. □

Note that the asymptotic normality of the allocation proportions can be derived as in [13, 14, 23] by adding suitable conditions of differentiability for the target $\boldsymbol{\pi}^*$ and, eventually, for φ.

COROLLARY 7.1. *Let the optimal compound target* $\boldsymbol{\pi}^*_\omega$ *be the desired allocation, then adopting the RDBCD in* (7.1), *as* n *tends to infinity*

$$\boldsymbol{\pi}_n \to \boldsymbol{\pi}^*_\omega \quad a.s. \quad \text{and} \quad \widehat{\boldsymbol{\pi}}^*_n \to \boldsymbol{\pi}^*_\omega \quad a.s.$$

$$\hat{\boldsymbol{\gamma}}_n \to \boldsymbol{\gamma} \quad a.s. \quad \text{and} \quad \sqrt{n}(\hat{\boldsymbol{\gamma}}_n - \boldsymbol{\gamma}) \to N(\mathbf{0}; \mathcal{M}^{-1}(\boldsymbol{\pi}^*_\omega)) \quad \text{in law.}$$

8. Finite sample properties. In order to perform some finite sample comparisons, we have conducted a simulation study by adopting the inferential criterion C1 and assuming as ethical weight function ω the cdf of $\chi^2_{(1)}$. Moreover, we have taken into account normal responses with $\sigma^2 = 1$ and two binary covariates with the previously used settings, that is, (i) two population scenarios, namely the uniform distribution $\mathcal{U}$ and the nonuniform one $\mathcal{NU}$ with $p(0,0) = 0.2$, $p(1,0) = 0.3$, $p(0,1) = 0.4$, $p(1,1) = 0.1$, (ii) two parameter settings: $(\alpha, \boldsymbol{\tau}^t) = (1,1,1,1)$ and $(\alpha, \boldsymbol{\tau}^t) = (-4,-1,3,3)$. The results come from $h = 500$ simulations with $m = 4$ and $n = 500$. Concerning the continuous randomization functions, we consider the CARA design φ_Z in (7.4) and the RDBCD in (7.5) with $k = 1$. As regards the discontinuous case, we perform the simulations adopting φ_{BAZ_2} in (7.6) and φ_{ERADE} in (7.2), where we put $\varepsilon = \rho = 2/3$, for homogeneity. Expectation and standard deviation (within brackets) of the proportion of allocations to treatment A are given in Tables 5–8.

In general, φ_Z in (7.4) is characterized by the strongest variability with respect to the other procedures, since it is based only on the current estimate of the target, independently on the actual allocation proportion. Moreover, as theoretically

TABLE 5

Expectation and standard deviation (within brackets) of the proportion of allocations to A under the uniform distribution $\mathcal{U}$ with $(\alpha, \boldsymbol{\tau}^t) = (1, 1, 1, 1)$, so that the optimal compound target is $\pi^*_\omega(0,0) = 0.593$, $\pi^*_\omega(1,0) = \pi^*_\omega(0,1) = 0.670$ and $\pi^*_\omega(1,1) = 0.771$

	$\boldsymbol{\pi_n(0,0)}$	$\boldsymbol{\pi_n(1,0)}$	$\boldsymbol{\pi_n(0,1)}$	$\boldsymbol{\pi_n(1,1)}$
φ_Z	0.592 (0.051)	0.667 (0.049)	0.666 (0.045)	0.764 (0.041)
φ_{BAZ_1}	0.592 (0.027)	0.667 (0.027)	0.670 (0.026)	0.768 (0.025)
φ_{BAZ_2}	0.591 (0.017)	0.668 (0.016)	0.669 (0.016)	0.769 (0.014)
φ_{ERADE}	0.589 (0.019)	0.665 (0.019)	0.666 (0.019)	0.764 (0.018)

shown in [23], the variability of this design increases as the representativeness of the strata decreases, and this behavior is also confirmed by φ_{ERADE}; see Tables 7 and 8. On the other hand, φ_{BAZ_1} and φ_{BAZ_2} tend to balance the variability of the allocation proportions between the different population strata. Indeed, the standard deviations of the design in the different patterns are similar, since the reinforced doubly adaptive biased coin design forces the closeness to the desired target the more the strata are under-represented.

Note that, in general, discontinuous randomization functions perform better with respect to the continuous ones. This is quite natural since, when the allocation proportion is around the target—in particular, for sufficiently large samples, due to the almost sure convergence—the continuous allocation procedures randomize the

TABLE 6

Expectation and standard deviation (within brackets) of the proportion of allocations to A under the uniform distribution $\mathcal{U}$ with $(\alpha, \boldsymbol{\tau}^t) = (-4, -1, 3, 3)$, so that the optimal compound target is $\pi^*_\omega(0,0) = 0.242$, $\pi^*_\omega(1,0) = 0.209$, $\pi^*_\omega(0,1) = 0.415$ and $\pi^*_\omega(1,1) = 0.585$

	$\boldsymbol{\pi_n(0,0)}$	$\boldsymbol{\pi_n(1,0)}$	$\boldsymbol{\pi_n(0,1)}$	$\boldsymbol{\pi_n(1,1)}$
φ_Z	0.250 (0.042)	0.217 (0.041)	0.416 (0.049)	0.582 (0.050)
φ_{BAZ_1}	0.244 (0.024)	0.211 (0.022)	0.412 (0.024)	0.585 (0.026)
φ_{BAZ_2}	0.244 (0.013)	0.212 (0.013)	0.415 (0.017)	0.585 (0.016)
φ_{ERADE}	0.251 (0.017)	0.217 (0.016)	0.417 (0.018)	0.584 (0.019)

TABLE 7

Expectation and standard deviation (within brackets) of the proportion of allocations to A under the nonuniform distribution $\mathcal{NU}$ with $(\alpha, \boldsymbol{\tau}^t) = (1, 1, 1, 1)$, so that the optimal compound target is $\pi^*_\omega(0,0) = 0.578$, $\pi^*_\omega(1,0) = 0.700$, $\pi^*_\omega(0,1) = 0.743$ and $\pi^*_\omega(1,1) = 0.646$

	$\boldsymbol{\pi_n(0,0)}$	$\boldsymbol{\pi_n(1,0)}$	$\boldsymbol{\pi_n(0,1)}$	$\boldsymbol{\pi_n(1,1)}$
φ_Z	0.576 (0.054)	0.696 (0.041)	0.732 (0.034)	0.651 (0.071)
φ_{BAZ_1}	0.577 (0.026)	0.699 (0.025)	0.739 (0.024)	0.646 (0.028)
φ_{BAZ_2}	0.577 (0.017)	0.698 (0.015)	0.740 (0.014)	0.646 (0.017)
φ_{ERADE}	0.576 (0.021)	0.694 (0.018)	0.738 (0.014)	0.640 (0.030)

assignment with probability close to the target, while the discontinuous ones tend to force the allocation in the same way at each step, even asymptotically.

Moreover, our simulation study points to the fact that φ_{BAZ_2} guarantees always a stable behavior and tends to have better performances w.r.t. φ_{ERADE}, especially for strongly under-represented strata. For instance, in the case of a nonuniform covariate distribution, when $(t_j, w_l) = (1, 1)$ the standard deviation of the allocation proportions under φ_{BAZ_2} is almost half of the φ_{ERADE}'s one (see Tables 7 and 8).

The same conclusions have been observed through further simulations, omitted here for brevity, with larger sample size. However, in this paper we decided to present the case of $n = 500$ in order to emphasize the evolution of our procedure, with respect to the others, especially for strongly under-represented strata (note

TABLE 8

Expectation and standard deviation (within brackets) of the proportion of allocations to A under the nonuniform distribution $\mathcal{NU}$ with $(\alpha, \boldsymbol{\tau}^t) = (-4, -1, 3, 3)$, so that the optimal compound target is $\pi^*_\omega(0,0) = 0.279$, $\pi^*_\omega(1,0) = 0.186$, $\pi^*_\omega(0,1) = 0.371$ and $\pi^*_\omega(1,1) = 0.534$

	$\boldsymbol{\pi_n(0,0)}$	$\boldsymbol{\pi_n(1,0)}$	$\boldsymbol{\pi_n(0,1)}$	$\boldsymbol{\pi_n(1,1)}$
φ_Z	0.284 (0.050)	0.197 (0.041)	0.377 (0.035)	0.539 (0.073)
φ_{BAZ_1}	0.279 (0.026)	0.188 (0.021)	0.373 (0.026)	0.535 (0.024)
φ_{BAZ_2}	0.280 (0.015)	0.189 (0.015)	0.373 (0.013)	0.534 (0.013)
φ_{ERADE}	0.286 (0.019)	0.195 (0.018)	0.375 (0.014)	0.533 (0.023)

that the expected number of patients within stratum $(1, 1)$ under the nonuniform distribution $\mathcal{NU}$ is 50).

9. Discussion. In the context of clinical trials for treatment comparisons, several different approaches have been proposed in the literature in order to provide a valid trade-off between ethical concerns and inferential precision (such as group sequential designs, interim analysis, etc.) and over the past 20 years there has been a growing stream of statistical papers on the topic of response-adaptive randomization; see, for instance, the seminal books of [12, 16]. Within this framework, in this paper we suggest a design strategy that combines efficiency and ethical gain for responses following a linear homoscedastic model. By using a compound optimization approach we derive optimal target allocations for the treatments that can be implemented via the adoption of a new class of CARA randomization procedure. Through the proposed methodology, the optimal compound allocations move away from balance (i.e., the optimal inferential target) toward the better treatment adaptively, on the basis of the treatment effects. Since joint balance implies marginal one, the proposed design strategy is robust with respect to possible misspecification of the model in terms of presence or absence of interactions among prognostic factors, or between treatments and covariates. Moreover, the proposed methodology is quite robust and performs well, even in the case of approximate homoscedasticity of the outcomes (perhaps after suitable transformations), as also pointed out by [3, 18]. On the other hand, in the case of heteroscedastic responses and, more generally, for generalized linear models, balance does not imply efficiency; our approach could still be applied, but with different inferential criteria (that could be optimized numerically) and different weight functions. Further research is needed on this topic.

APPENDIX

A.1. Proof of Proposition 3.1.

C1. For the sake of simplicity in this Appendix, we will often omit the subscripts indicating the dimensions of vectors and matrices. Let $\widetilde{\mathbf{M}} = n\mathbf{M}$, then

$$\det \widetilde{\mathbf{M}} = \det \left(\begin{array}{cc|cc} \displaystyle\sum_{i=1}^{n} \delta_i & \boldsymbol{\delta}^t \mathbf{F} & 0 & \mathbf{0}_{1\times p} \\ \mathbf{F}^t \boldsymbol{\delta} & \mathbf{F}^t \boldsymbol{\Delta} \mathbf{F} & \mathbf{0}_{p\times 1} & \mathbf{0}_{p\times p} \\ \hline 0 & \mathbf{0}_{1\times p} & n - \displaystyle\sum_{i=1}^{n} \delta_i & (\mathbf{1} - \boldsymbol{\delta})^t \mathbf{F} \\ \mathbf{0}_{p\times 1} & \mathbf{0}_{p\times p} & \mathbf{F}^t (\mathbf{1} - \boldsymbol{\delta}) & \mathbf{F}^t (\mathbf{I} - \boldsymbol{\Delta}) \mathbf{F} \end{array} \right).$$

Let $\boldsymbol{\Omega}_A = \mathbf{F}^t \boldsymbol{\Delta} \mathbf{F}$ and $\boldsymbol{\Omega}_B = \mathbf{F}^t (\mathbf{I} - \boldsymbol{\Delta}) \mathbf{F}$, and we obtain that

$$\det \widetilde{\mathbf{M}} = \det \boldsymbol{\Omega}_A \left\{ \sum_{i=1}^{n} \delta_i - \boldsymbol{\delta}^t \mathbf{F} \boldsymbol{\Omega}_A^{-1} \mathbf{F}^t \boldsymbol{\delta} \right\}$$

$$\times \det \boldsymbol{\Omega}_B \left\{ \left(n - \sum_{i=1}^{n} \delta_i \right) - (\mathbf{1} - \boldsymbol{\delta})^t \mathbf{F} \boldsymbol{\Omega}_B^{-1} \mathbf{F}^t (\mathbf{1} - \boldsymbol{\delta}) \right\}.$$

Let now $\boldsymbol{\delta}^t \mathbf{F} = (\widetilde{\mathbf{N}}_{\mathbb{T}}^t, \widetilde{\mathbf{N}}_{\mathbb{W}}^t, \widetilde{\mathbf{N}}_{\mathbb{T}\otimes\mathbb{W}}^t)$, where $\widetilde{\mathbf{N}}_{\mathbb{T}}^t = (\widetilde{N}(t_1), \ldots, \widetilde{N}(t_J))$, $\widetilde{\mathbf{N}}_{\mathbb{W}}^t = (\widetilde{N}(w_1), \ldots, \widetilde{N}(w_L))$ with $\widetilde{N}(t_j) = \sum_{l=0}^{L} \widetilde{N}(j,l)$ and $\widetilde{N}(w_l) = \sum_{j=0}^{J} \widetilde{N}(j,l)$, and $\widetilde{\mathbf{N}}_{\mathbb{T}\otimes\mathbb{W}}^t = (\widetilde{N}(1,1), \ldots, \widetilde{N}(1,L), \ldots, \widetilde{N}(J,1), \ldots, \widetilde{N}(J,L))$. Clearly, $\widetilde{N}(t_j)$ and $\widetilde{N}(w_l)$ are the number of subjects assigned to treatment A within category t_j of T $(j = 0, \ldots, J)$ and w_l of W $(l = 0, \ldots, L)$, respectively. Also, let $\widetilde{\mathbf{N}}_{t_j\otimes\mathbb{W}}^t = (\widetilde{N}(j,1), \ldots, \widetilde{N}(j,L))$ and $\widetilde{\mathbf{N}}_{\mathbb{T}\otimes w_l}^t = (\widetilde{N}(1,l), \ldots, \widetilde{N}(J,l))$. Then, the matrix $\boldsymbol{\Omega}_A$ can be partitioned as follows:

$$\boldsymbol{\Omega}_A = \left(\begin{array}{c|c} \mathbf{A} & \mathbf{B} \\ \hline \mathbf{B}^t & \mathbf{C} \end{array} \right), \tag{A.1}$$

where

$$\mathbf{A} = \operatorname{diag}(\widetilde{\mathbf{N}}_{\mathbb{T}}, \widetilde{\mathbf{N}}_{\mathbb{W}}) + \left(\begin{array}{ccc|c} & \mathbf{0}_{J\times J} & & \widetilde{\mathbf{N}}_{t_1\otimes\mathbb{W}}^t \\ & & & \vdots \\ & & & \widetilde{\mathbf{N}}_{t_J\otimes\mathbb{W}}^t \\ \hline \widetilde{\mathbf{N}}_{t_1\otimes\mathbb{W}} & \cdots & \widetilde{\mathbf{N}}_{t_J\otimes\mathbb{W}} & \mathbf{0}_{L\times L} \end{array} \right),$$

$$\mathbf{B} = \begin{pmatrix} \widetilde{\mathbf{N}}_{t_1\otimes\mathbb{W}}^t & \mathbf{0} & \mathbf{0} & \cdots & \mathbf{0} \\ \mathbf{0} & \widetilde{\mathbf{N}}_{t_2\otimes\mathbb{W}}^t & \mathbf{0} & \cdots & \mathbf{0} \\ \vdots & & \ddots & & \mathbf{0} \\ \mathbf{0} & \mathbf{0} & \cdots & & \widetilde{\mathbf{N}}_{t_J\otimes\mathbb{W}}^t \\ \operatorname{diag}(\widetilde{\mathbf{N}}_{t_1\otimes\mathbb{W}}) & \operatorname{diag}(\widetilde{\mathbf{N}}_{t_2\otimes\mathbb{W}}) & \cdots & & \operatorname{diag}(\widetilde{\mathbf{N}}_{t_J\otimes\mathbb{W}}) \end{pmatrix}$$

and $\mathbf{C} = \operatorname{diag}(\widetilde{\mathbf{N}}_{\mathbb{T}\otimes\mathbb{W}})$, where $\mathbf{0}_{K\times K}$ is the K-dim zero matrix. Thus,

$$\boldsymbol{\Omega}_A^{-1} = \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array} \right) + \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \boldsymbol{\Gamma}^{-1} (\mathbf{I}_{J+L}, -\mathbf{B}\mathbf{C}^{-1}), \tag{A.2}$$

where $\boldsymbol{\Gamma} = \mathbf{A} - \mathbf{B}\mathbf{C}^{-1}\mathbf{B}^t = \operatorname{diag}(\widetilde{\mathbf{N}}_{\mathbb{T}\otimes w_0}, \widetilde{\mathbf{N}}_{t_0\otimes\mathbb{W}})$. Note that $\boldsymbol{\Omega}_A$ is nonsingular if and only if $\mathbf{C}$ and $\boldsymbol{\Gamma}$ are nonsingular and $\det \boldsymbol{\Omega}_A = \det \mathbf{C} \cdot \det \boldsymbol{\Gamma} = \prod_{j,l=1}^{J,L} \widetilde{N}(j,l) \prod_{j=1}^{J} \widetilde{N}(j,0) \prod_{l=1}^{L} \widetilde{N}(0,l)$. From (A.2) it follows that

$$\boldsymbol{\delta}^t \mathbf{F} \boldsymbol{\Omega}_A^{-1} \mathbf{F}^t \boldsymbol{\delta} = \boldsymbol{\delta}^t \mathbf{F} \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array} \right) \mathbf{F}^t \boldsymbol{\delta} + \boldsymbol{\delta}^t \mathbf{F} \begin{pmatrix} \mathbf{I}_{J+L} \\ -\mathbf{C}^{-1}\mathbf{B}^t \end{pmatrix} \boldsymbol{\Gamma}^{-1} (\mathbf{I}_{J+L}, -\mathbf{B}\mathbf{C}^{-1}) \mathbf{F}^t \boldsymbol{\delta},$$

where

$$\boldsymbol{\delta}^t \mathbf{F} \left(\begin{array}{c|c} \mathbf{0} & \mathbf{0} \\ \hline \mathbf{0} & \mathbf{C}^{-1} \end{array} \right) \mathbf{F}^t \boldsymbol{\delta} = \sum_{j=1}^{J} \sum_{l=1}^{L} \widetilde{N}(j,l)$$

and

$$\boldsymbol{\delta}^t\mathbf{F}\begin{pmatrix}\mathbf{I}_{J+L}\\ -\mathbf{C}^{-1}\mathbf{B}^t\end{pmatrix}\boldsymbol{\Gamma}^{-1}(\mathbf{I}_{J+L},-\mathbf{B}\mathbf{C}^{-1})\mathbf{F}^t\boldsymbol{\delta}=\sum_{j=1}^{J}\widetilde{N}(j,0)+\sum_{l=1}^{L}\widetilde{N}(0,l),$$

since

$$\mathbf{B}\mathbf{C}^{-1}=\begin{pmatrix}\mathbf{1}_L^t & \mathbf{0} & \cdots & \mathbf{0}\\ \mathbf{0} & \mathbf{1}_L^t & \cdots & \mathbf{0}\\ \vdots & & \ddots & \vdots\\ \mathbf{0} & \mathbf{0} & \cdots & \mathbf{1}_L^t\\ \mathbf{I}_L & \mathbf{I}_L & \cdots & \mathbf{I}_L\end{pmatrix} \tag{A.3}$$

and

$$\boldsymbol{\Gamma}^{-1}\mathbf{B}\mathbf{C}^{-1}=\begin{pmatrix}\widetilde{N}(1,0)^{-1}\mathbf{1}_L^t & \mathbf{0} & \cdots & \mathbf{0}\\ \mathbf{0} & \widetilde{N}(2,0)^{-1}\mathbf{1}_L^t & \cdots & \mathbf{0}\\ \vdots & & \ddots & \vdots\\ \mathbf{0} & & \cdots & \widetilde{N}(J,0)^{-1}\mathbf{1}_L^t\\ \operatorname{diag}(\widetilde{N}_{t_0\otimes\mathbb{W}})^{-1} & \operatorname{diag}(\widetilde{N}_{t_0\otimes\mathbb{W}})^{-1} & \cdots & \operatorname{diag}(\widetilde{N}_{t_0\otimes\mathbb{W}})^{-1}\end{pmatrix}. \tag{A.4}$$

Therefore, $\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}\mathbf{F}^t\boldsymbol{\delta}=\sum_{j=1}^{J}\sum_{l=1}^{L}\widetilde{N}(j,l)+\sum_{j=1}^{J}\widetilde{N}(j,0)+\sum_{l=1}^{L}\widetilde{N}(0,l)$, and consequently $\sum_{i=1}^{n}\delta_i-\boldsymbol{\delta}^t\mathbf{F}(\boldsymbol{\Omega}_A)^{-1}\mathbf{F}^t\boldsymbol{\delta}=\widetilde{N}(0,0)$. Hence,

$$\det\widetilde{\mathbf{M}}=\prod_{j=0}^{J}\prod_{l=0}^{L}N(j,l)^2\pi(j,l)[1-\pi(j,l)]$$

and thus (3.4) follows directly.

C2. Note that $\widetilde{\mathbf{M}}^{-1}$ can be partitioned as follows:

$$\widetilde{\mathbf{M}}^{-1}=\left(\begin{array}{c|c}\widetilde{\mathbf{M}}_{11}^{-1} & \widetilde{\mathbf{M}}_{12}^{-1}\\ \hline (\widetilde{\mathbf{M}}_{12}^{-1})^t & \widetilde{\mathbf{M}}_{22}^{-1}\end{array}\right),$$

where $\widetilde{\mathbf{M}}_{11}^{-1}$ is given by

$$\left[\begin{pmatrix}\sum_{i=1}^{n}\delta_i & 0\\ 0 & n-\sum_{i=1}^{n}\delta_i\end{pmatrix}-\begin{pmatrix}\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}\mathbf{F}^t\boldsymbol{\delta} & 0\\ 0 & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F}\boldsymbol{\Omega}_B^{-1}\mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta})\end{pmatrix}\right]^{-1}$$

$$=\begin{pmatrix}N(0,0)\pi(0,0) & 0\\ 0 & N(0,0)[1-\pi(0,0)]\end{pmatrix}^{-1},$$

$$\widetilde{\mathbf{M}}_{12}^{-1} = -\widetilde{\mathbf{M}}_{11}^{-1} \begin{pmatrix} \boldsymbol{\delta}^t\mathbf{F} & \mathbf{0} \\ \mathbf{0} & (\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F} \end{pmatrix} \begin{pmatrix} \boldsymbol{\Omega}_A^{-1} & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\Omega}_B^{-1} \end{pmatrix},$$

and

$$\widetilde{\mathbf{M}}_{22}^{-1} = \begin{pmatrix} \boldsymbol{\Omega}_A^{-1} & \mathbf{0} \\ 0 & \boldsymbol{\Omega}_B^{-1} \end{pmatrix} \left[\mathbf{I}_{2p} - \begin{pmatrix} \mathbf{F}^t\boldsymbol{\delta} & \mathbf{0} \\ \mathbf{0} & \mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta}) \end{pmatrix} \widetilde{\mathbf{M}}_{12}^{-1} \right].$$

Thus, $\det(\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D}) = \det\mathbf{M}_{22}^{-1}$, which is given by

$$\det\boldsymbol{\Omega}_A^{-1} \det\left[\mathbf{I}_p + \frac{\mathbf{F}^t\boldsymbol{\delta}\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}}{N(0,0)\pi(0,0)}\right] \det\boldsymbol{\Omega}_B^{-1} \det\left[\mathbf{I}_p + \frac{\mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta})(\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F}\boldsymbol{\Omega}_B^{-1}}{N(0,0)[1-\pi(0,0)]}\right].$$

Applying Sylvester's determinant theorem, we obtain that

$$\begin{aligned} \det\boldsymbol{\Omega}_A^{-1} \det\left[\mathbf{I}_p + \frac{\mathbf{F}^t\boldsymbol{\delta}\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}}{N(0,0)\pi(0,0)}\right] &= \det\boldsymbol{\Omega}_A^{-1}\left(1 + \frac{\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}\mathbf{F}^t\boldsymbol{\delta}}{N(0,0)\pi(0,0)}\right) \\ &= \frac{\sum_{i=1}^n \delta_i}{\prod_{j=0}^J \prod_{l=0}^L N(j,l)\pi(j,l)}. \end{aligned}$$

Analogously for treatment B, so that (3.5) follows easily after simple algebra.

C3–C4. Clearly $\operatorname{tr}(n^{-1}\mathbf{D}^t\mathbf{M}^{-1}\mathbf{D}) = \operatorname{tr}\widetilde{\mathbf{M}}_{22}^{-1}$, so criterion C3 is given by

$$\begin{aligned} &\sigma^2 \operatorname{tr}\left(\boldsymbol{\Omega}_A^{-1} + \frac{1}{N(0,0)\pi(0,0)}\boldsymbol{\Omega}_A^{-1}\mathbf{F}^t\boldsymbol{\delta}\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}\right) \\ &\quad + \sigma^2 \operatorname{tr}\left(\boldsymbol{\Omega}_B^{-1} + \frac{1}{N(0,0)[1-\pi(0,0)]}\boldsymbol{\Omega}_B^{-1}\mathbf{F}^t(\mathbf{1}-\boldsymbol{\delta})(\mathbf{1}-\boldsymbol{\delta})^t\mathbf{F}\boldsymbol{\Omega}_B^{-1}\right). \end{aligned} \tag{A.5}$$

Note that $\operatorname{tr}(n^{-1}\sigma^2\mathbf{E}^t\mathbf{M}^{-1}\mathbf{E})$ coincides with (A.5) and thus C4 is equal to C3. Since

$$\boldsymbol{\Omega}_A^{-1} = \left(\begin{array}{c|c} \boldsymbol{\Gamma}^{-1} & -\boldsymbol{\Gamma}^{-1}\mathbf{B}\mathbf{C}^{-1} \\ \hline -\mathbf{C}^{-1}\mathbf{B}^t\boldsymbol{\Gamma}^{-1} & \mathbf{C}^{-1} + \mathbf{C}^{-1}\mathbf{B}^t\boldsymbol{\Gamma}^{-1}\mathbf{B}\mathbf{C}^{-1} \end{array}\right),$$

we obtain $\operatorname{tr}(\boldsymbol{\Omega}_A^{-1}) = \operatorname{tr}(\boldsymbol{\Gamma}^{-1}) + \operatorname{tr}(\mathbf{C}^{-1}) + \operatorname{tr}(\mathbf{C}^{-1}\mathbf{B}^t\boldsymbol{\Gamma}^{-1}\mathbf{B}\mathbf{C}^{-1})$. From (A.3) and (A.4), it follows that

$$\operatorname{tr}(\mathbf{C}^{-1}\mathbf{B}^t\boldsymbol{\Gamma}^{-1}\mathbf{B}\mathbf{C}^{-1}) = \sum_{j=1}^J \sum_{l=1}^L \left(\frac{1}{\widetilde{N}(j,0)} + \frac{1}{\widetilde{N}(0,l)}\right) = \sum_{j=1}^J \frac{L}{\widetilde{N}(j,0)} + \sum_{l=1}^L \frac{J}{\widetilde{N}(0,l)},$$

and thus $\operatorname{tr}(\boldsymbol{\Omega}_A^{-1})$ is

$$\sum_{j=1}^J \sum_{l=1}^L \left(\frac{1}{\widetilde{N}(0,l)} + \frac{1}{\widetilde{N}(j,0)}\right) + \sum_{j=1}^J \sum_{l=1}^L \left(\frac{1}{\widetilde{N}(j,l)}\right) + \sum_{j=1}^J \sum_{l=1}^L \left(\frac{1}{\widetilde{N}(0,l)} + \frac{1}{\widetilde{N}(j,0)}\right).$$

Moreover, from (A.2), (A.3) and (A.4) we obtain $\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1} = (\mathbf{1}_{J+L}^t, -\mathbf{1}_{J\cdot L}^t)$ and thus $\boldsymbol{\Omega}_A^{-1}\mathbf{F}^t\boldsymbol{\delta}\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}$ has unitary diagonal elements, so that $\operatorname{tr}(\boldsymbol{\Omega}_A^{-1}\mathbf{F}^t\boldsymbol{\delta}\boldsymbol{\delta}^t\mathbf{F}\boldsymbol{\Omega}_A^{-1}) = J + L + J\cdot L$. Analogously for treatment B.

A.2. Proof of Theorem 7.1. As regards the first statement (7.7), at each stratum (t_j, w_l) we will prove the convergence of both $\pi_n(j,l)$ and $\widehat{\pi}_n^*(j,l)$ to the target $\pi^*(j,l)$; for ease of notation we will often omit the subscript (j,l) assuming that we are fixing the stratum (t_j, w_l). Let $\mathfrak{F}_n = \sigma(Y_1, \ldots, Y_n, \delta_1, \ldots, \delta_n, Z_1, \ldots, Z_n)$ denote the σ-field representing the history of the trial, with $\mathfrak{F}_0$ the trivial σ-field, and $\mathfrak{G}_n = \sigma(\mathfrak{F}_n, Z_{n+1})$. Moreover, let $\Delta M_i = [\delta_i - E(\delta_i|\mathfrak{G}_{i-1})]\mathbb{1}_{\{Z_i=(t_j,w_l)\}}$, then $\{\Delta M_i; i \geq 1\}$ is a sequence of bounded martingale differences with $|\Delta M_i| \leq 1$ for any $i \geq 1$; thus the sequence $\{M_n = \sum_{i=1}^n \Delta M_i; \mathfrak{G}_n\}$ is a martingale with $\sum_{k=1}^n E[(\Delta M_i)^2|\mathfrak{G}_{k-1}] \leq N_n$.

Let $l_n = \max\{s : 2m+1 \leq s \leq n, \widetilde{N}_s - N_s\widehat{\pi}_s^* \leq 0\}$, with $\max \varnothing = 2m$, and note that

$$\begin{aligned}
\widetilde{N}_n &= \widetilde{N}_{l_n+1} + \sum_{k=l_n+2}^{n} \Delta M_k + \sum_{k=l_n+2}^{n} E(\delta_k|\mathfrak{G}_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&\leq \widetilde{N}_{l_n} + 1 + M_n - M_{l_n+1} + \sum_{k=l_n+2}^{n} \varphi(\pi_{k-1}; \widehat{\pi}_{k-1}^*; \widehat{p}_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&< \widetilde{N}_{l_n} + 1 + M_n - M_{l_n+1} + \sum_{k=l_n+2}^{n} \widehat{\pi}_{k-1}^*\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&= \widetilde{N}_{l_n} + 1 + M_n - M_{l_n+1} + \sum_{k=1}^{n} \widehat{\pi}_{k-1}^*\mathbb{1}_{\{Z_k=(t_j,w_l)\}} - \sum_{k=1}^{l_n+1} \widehat{\pi}_{k-1}^*\mathbb{1}_{\{Z_k=(t_j,w_l)\}},
\end{aligned}$$

since for any $i \geq l_n + 1$, $\varphi(\pi_i; \widehat{\pi}_i^*; \widehat{p}_i) < \widehat{\pi}_i^* < \pi_i$; whereas $\widetilde{N}_{l_n} \leq N_{l_n}\widehat{\pi}_{l_n}^*$ and thus

$$\begin{aligned}
\widetilde{N}_n - N_n\widehat{\pi}_n^* \leq &\left(N_{l_n}\widehat{\pi}_{l_n}^* - \sum_{k=1}^{l_n+1} \widehat{\pi}_{k-1}^*\mathbb{1}_{\{Z_k=(t_j,w_l)\}}\right) + M_n - M_{l_n+1} + 1 \\
&- \left(N_n\widehat{\pi}_n^* - \sum_{k=1}^{n} \widehat{\pi}_{k-1}^*\mathbb{1}_{\{Z_k=(t_j,w_l)\}}\right).
\end{aligned}$$

Since $p(j,l) > 0$ for each stratum (t_j, w_l), then as $n \to \infty$, $N_n \to \infty$ a.s. and therefore $N_n^{-1}M_n \to 0$ a.s.; see, for instance, [21]. Furthermore, as $n \to \infty$, $\widehat{\mathbf{p}}_n \to \mathbf{p}$ a.s. and at least one of the the number of assignments to the treatments, namely $\widetilde{N}_n$ and $(N_n - \widetilde{N}_n)$, tends to infinity a.s. As showed in [14], in any case $\widehat{\boldsymbol{\gamma}}_n$ has finite limit so that, from the properties of π^*, there exists a $v \in (0,1)$ such that

$$\widehat{\pi}_n^* \to v \qquad \text{a.s.} \tag{A.6}$$

and so

$$\widehat{\pi}_n^* - \frac{\sum_{k=1}^n \widehat{\pi}_{k-1}^*\mathbb{1}_{\{Z_k=(t_j,w_l)\}}}{\sum_{k=1}^n \mathbb{1}_{\{Z_k=(t_j,w_l)\}}} \to 0 \qquad \text{a.s.}$$

As $n \to \infty$, then $l_n \to \infty$ or $\sup_n l_n < \infty$; in either case,

$$\widehat{\pi}^*_{l_n} \frac{N_{l_n}}{N_n} - \frac{\sum_{k=1}^{l_n+1} \widehat{\pi}^*_{k-1} \mathbb{1}_{\{Z_k=(t_j,w_l)\}}}{\sum_{k=1}^{n} \mathbb{1}_{\{Z_k=(t_j,w_l)\}}} \to 0 \qquad \text{a.s.}$$

and therefore

$$(\pi_n - \widehat{\pi}^*_n)^+ \to 0 \qquad \text{a.s.} \tag{A.7}$$

Let $\lambda_n = \max\{s : 2m+1 \le s \le n, (N_s - \widetilde{N}_s) - N_s(1-\widehat{\pi}^*_s) \le 0\}$, for any $i \ge \lambda_n + 1$, we have $\varphi(\pi_i; \widehat{\pi}^*_i; \widehat{p}_i) = 1 - \varphi(1-\pi_i; 1-\widehat{\pi}^*_i; \widehat{p}_i) > \widehat{\pi}^*_i > \pi_i$. Then,

$$\begin{aligned}
N_n - \widetilde{N}_n &= N_{\lambda_n+1} - \widetilde{N}_{\lambda_n+1} + \sum_{k=\lambda_n+2}^{n} E\big((1-\delta_k)|\mathfrak{G}_{k-1}\big)\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&\quad + \sum_{k=\lambda_n+2}^{n} \big[(1-\delta_k) - E\big((1-\delta_k)|\mathfrak{G}_{k-1}\big)\big]\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&\le N_{\lambda_n} + 1 - \widetilde{N}_{\lambda_n} - (M_n - M_{\lambda_n+1}) \\
&\quad + \sum_{k=\lambda_n+2}^{n} \varphi(1-\pi_{k-1}; 1-\widehat{\pi}^*_{k-1}; \widehat{p}_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&< N_{\lambda_n} + 1 - \widetilde{N}_{\lambda_n} - (M_n - M_{\lambda_n+1}) + \sum_{k=\lambda_n+2}^{n} (1-\widehat{\pi}^*_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&= N_{\lambda_n} + 1 - \widetilde{N}_{\lambda_n} - (M_n - M_{\lambda_n+1}) + \sum_{k=1}^{n} (1-\widehat{\pi}^*_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \\
&\quad - \sum_{k=1}^{\lambda_n+1} (1-\widehat{\pi}^*_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}}.
\end{aligned}$$

Hence,

$$\begin{aligned}
&(N_n - \widetilde{N}_n) - N_n(1-\widehat{\pi}^*_n) \\
&\quad \le \left\{ N_{\lambda_n}(1-\widehat{\pi}^*_{\lambda_n}) - \sum_{k=1}^{\lambda_n+1} (1-\widehat{\pi}^*_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \right\} \\
&\qquad + 1 - (M_n - M_{\lambda_n+1}) - \left\{ N_n(1-\widehat{\pi}^*_n) - \sum_{k=1}^{n} (1-\widehat{\pi}^*_{k-1})\mathbb{1}_{\{Z_k=(t_j,w_l)\}} \right\},
\end{aligned}$$

so that

$$\big((1-\pi_n) - (1-\widehat{\pi}^*_n)\big)^+ \to 0 \qquad \text{a.s.} \tag{A.8}$$

From (A.7) and (A.8), as n tends to infinity

$$\pi_n - \widehat{\pi}_n^* \to 0 \qquad \text{a.s.}$$

and by (A.6)

$$\lim_{n\to\infty} \pi_n = \lim_{n\to\infty} \widehat{\pi_n^*} = v \qquad \text{a.s.}$$

Since $0 < v < 1$, then $0 < 1 - v < 1$ and thus

$$\lim_{n\to\infty} \widetilde{N}_n \to \infty \qquad \text{a.s.} \quad \text{and} \quad \lim_{n\to\infty} (N_n - \widetilde{N}_n) \to \infty \qquad \text{a.s.}$$

Therefore, $\lim_{n\to\infty} \widehat{\boldsymbol{\gamma}}_n \to \boldsymbol{\gamma}$ a.s. and from the continuity of the target $\lim_{n\to\infty} \widehat{\pi}_n^* = \pi^* = v$ a.s., that is,

$$\lim_{n\to\infty} \pi_n = \pi^* \qquad \text{a.s.} \tag{A.9}$$

Taking into account the average information matrix $\mathbf{M}$ in (2.3), from (A.9) and the proof of Proposition 3.1 it follows that

$$\lim_{n\to\infty} n^{-1} \sum_{i=1}^{n} \delta_i = \sum_{j=0}^{J} \sum_{l=0}^{L} \pi^*(j,l) p(j,l) \qquad \text{a.s.}$$

$$\lim_{n\to\infty} n^{-1} \boldsymbol{\delta}^t \mathbf{F} = \widetilde{\boldsymbol{\pi}}^{*t} \qquad \text{a.s.} \quad \text{and} \quad \lim_{n\to\infty} n^{-1} \mathbf{F}^t \boldsymbol{\Delta} \mathbf{F} = \boldsymbol{\mathcal{M}}^A \quad \text{a.s.}$$

Thus, as n goes to infinity the information matrix converges almost surely to $\boldsymbol{\mathcal{M}}(\boldsymbol{\pi}^*)$, which is nonsingular since $\sum_{j=0}^{J} \sum_{l=0}^{L} \pi^*(j,l) p(j,l) \in (0,1)$, $\boldsymbol{\mathcal{M}}^A$ and $\boldsymbol{\mathcal{M}}^B$ are nonsingular, and the matrix

$$\begin{pmatrix} \sum_{j=0}^{J} \sum_{l=0}^{L} \pi^*(j,l) p(j,l) & 0 \\ 0 & 1 - \sum_{j=0}^{J} \sum_{l=0}^{L} \pi^*(j,l) p(j,l) \end{pmatrix}$$

$$- \begin{pmatrix} \boldsymbol{\delta}^t \mathbf{F} & \mathbf{0} \\ \mathbf{0} & (\mathbf{1} - \boldsymbol{\delta})^t \mathbf{F} \end{pmatrix} \begin{pmatrix} \boldsymbol{\mathcal{M}}^A & \mathbf{0} \\ \mathbf{0} & \boldsymbol{\mathcal{M}}^B \end{pmatrix}^{-1} \begin{pmatrix} \mathbf{F}^t \boldsymbol{\delta} & \mathbf{0} \\ \mathbf{0} & \mathbf{F}^t (\mathbf{1} - \boldsymbol{\delta}) \end{pmatrix}$$

$$= \begin{pmatrix} \pi^*(0,0) p(0,0) & 0 \\ 0 & 1 - \pi^*(0,0) p(0,0) \end{pmatrix}$$

is nonsingular too, since $\pi^*(0,0) p(0,0) \in (0,1)$. Thus, the asymptotic normality of $\widehat{\boldsymbol{\gamma}}_n$ follows directly.

Acknowledgments. The authors thank the referees and the Associate Editor for their helpful comments, which led to a substantial improved version of the paper.

SUPPLEMENTARY MATERIAL

Supplement to "Multi-objective optimal designs in comparative clinical trials with covariates: the reinforced doubly adaptive biased coin design" (DOI: 10.1214/12-AOS1007SUPP; .pdf). An online supplementary file contains the extension of inferential criteria C1–C5 to the case of several covariates.

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