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Journal Title
XX(X):1–29

DOI: 10.1177/ToBeAssigned
www.sagepub.com/
SAGE

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Abstract

Enrichment designs with a continuous biomarker require the estimation of a threshold to determine the subpopulation benefitting from the treatment. This paper provides the optimal allocation for inference in a two-stage enrichment design for treatment comparisons when a continuous biomarker is suspected to affect patient response. Several design criteria, associated with different trial objectives, are optimized under balanced or Neyman allocation and under equality of the first two empirical biomarker's moments. Moreover, we propose a new covariate-adaptive randomization procedure that converges to the optimum with the fastest available rate. Theoretical and simulation results show that this strategy improves the efficiency of a two-stage enrichment clinical trial, especially with smaller sample sizes and under heterogeneous responses.

Keywords

Biomarker; Covariate-adaptive randomization; Design of experiments; Enrichment; Precision medicine.

1 Introduction

The identification of a benefitting subpopulation for a targeted therapy represents a critical facet of precision medicine. Clinical trials that were once designed simply to determine the average effect of the treatment among all diseased patients, must be adapted to incorporate heterogeneity induced by genetic and other biomarkers. Many biomarkers are dichotomous (e.g., presence or absence) while others are continuous (e.g., serum levels) and require estimation procedures to determine an appropriate

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discriminant to identify the benefitting subpopulation. In this latter case, several strategies have been adopted. The most popular strategy consists of discretizing the continuous biomarker with a cutoff elicited by the clinicians [1,2]. Others have proposed to set the cutoff equal to a quantile of the biomarker distribution [3] while much more limited work has been done to estimate the threshold directly on a continuous scale [4–6]. This is the approach taken in this paper.

Determining the threshold of a continuous biomarker is often a requirement of precision medicine. Its utility arises from the subgroup analysis commonly carried out at the end of each clinical trial and extends to adaptive enrichment designs [6,7]. Enrichment can be traced to Simon and Maitournam's [8] and Wang et al [9], but the idea likely originated in oncology and several earlier papers [10,11]. An initial phase of a clinical trial is conducted on a full population and, at the conclusion of the first phase, the biomarker threshold is determined and consequently the benefitting patient subgroup. That subpopulation is enrolled in a second phase, thus improving the likelihood of a therapy's success.

For instance, in studies for depression, due to the complexity of this disorder, a number of biomarkers are indicated in the reference literature to identify more treatment-responsive subgroups [12,13]. In a randomized controlled trial to compare interpersonal psychotherapy (IPT) and cognitive behavioral therapy (CT), no significant difference was found between IPT and CT in terms of improvement in the disease severity score [1] (measured by MADRS, i.e., Montgomery-Asberg Depression Rating Scale). However, further analysis suggested that in more depressed patients (baseline MADRS score > 30), CT induced a significantly better response than IPT. In the SMART-AV trial [14], subjects with medically refractive heart failure with severe left ventricular systolic dysfunction were recruited and a certain type of defibrillator has been implanted. To find out the effect of optimizing the atrioventricular delay, two methods (treatments) were compared against a fixed delay of $120ms$ (control). The primary endpoint, i.e., left ventricular end-systolic volume, did not significantly differ between the groups but previous scientific knowledge [15] suggested that patients with a QRS (i.e., waves Q, R and S of the electrocardiogram) duration smaller than $150ms$ could be more likely to benefit from the treatments.

Despite the well-known potential benefits of an enrichment design, the complex experimental framework poses new challenges and several complications need to be taken into account, even leading to questioning whether and when it is worth enriching [6]. One of the major concerns of these procedures is how "to make optimal decisions for updating the enrollment criteria" [16], which is even more complicated when the estimation of the threshold of a continuous biomarker is involved. This is an important aspect of enrichment with potentially disastrous consequences if this is not done accurately [17] and this work provides the optimal design for inference on the threshold of a quantitative biomarker. Almost all the recent papers on enrichment have been dedicated to analysis, while the optimal design problem has received very little attention [6]; indeed, most of the existing proposals deal with dichotomous markers [18] and balance the allocation among the treatment groups.

Before using a biomarker to drive the design of an enrichment study, an adequate understanding of its relationship with the treatment should be reached. Advances in biomedicine and disease biology have led to an increasing knowledge of the mechanism of action of new pharmaceuticals. However, even if a biomarker is claimed to affect the response of patients to treatments, its validity should be assessed in a specific study. A biomarker can be prognostic or predictive. A prognostic biomarker is correlated only with the outcome and a predictive biomarker is correlated with the outcome and the treatment. Frieri et al. [17] gauge the predictive nature of the biomarker with the correlation coefficient of a bivariate normal model (see also Lin et al. [19]). Spencer et al. [4] use a beta-binomial prediction model and Jian et al. [20] use

the hazard ratio for survival outcomes. In this paper, we use the treatment-by-covariate interaction from a linear model, with both homoscedastic and heteroscedastic outcomes. There are many clinical trials where, especially in the design phase, the primary outcome can be assumed normally distributed (like, e.g., depression rating scales, change in tumor size[21]). In many other experimental settings, the responses can be treated as approximately normal after suitable transformation or when they refer to measurements of, for instance, physical and biological characteristics[22]. The study on depression comparing IPT and CT and the SMART-AV trial can be taken as motivating examples.

The idea of finding optimal treatment allocation in a clinical trial with covariates originated in Atkinson[23]. Only in his 2015 paper[24], were treatment-by-covariate interactions explored. This paper differs from our work in that he assumes that the investigator has control over the values of the covariates, whereas in most clinical trials the covariates are inherent characteristics of the enrolled subjects, and cannot be controlled except by restricting eligibility.

Azriel, et al.[25] propose a design strategy with the aim of selecting the treatment with the best expected response for a patient with certain covariates. They use the regret of a linear model as their design criterion to minimize and found that the allocation rates depend on a set of given covariates only when more than two treatments are compared. Under some assumptions, their optimal allocation problem is equivalent to minimize the variance of the threshold estimator determining the benefitting subpopulation, asymptotically. However, they do not consider an adaptive setting and the enrichment scenario.

In a two-arm clinical trial, we derive the optimal design for estimating/testing whether a benefitting population exists; then we address optimal treatment allocation for the efficient estimation of the biomarker threshold defining such benefitting subgroup. Section 3 deals with homoscedastic responses: according to whether the interest is on the whole vector of model parameters or on a subset, the D- and A- optimality criteria are optimized under the equality of i) the allocation proportions to the two arms and ii) the first two empirical moments of the biomarker distributions. Under heteroscedasticity, balanced treatment assignment should be replaced by Neyman allocation (Section 4). While we derive the theoretical optimal designs, in practice a randomization procedure must be used to implement these designs in a clinical trial[26]. In Section 5, we describe the types of randomization procedures necessary to achieve the optimal design, at least asymptotically. These designs are from the class of covariate-adaptive (CA) randomization procedures that balance the empirical moments of covariates asymptotically[27]. In particular, we introduce a new CA randomization procedure that targets the optimal allocation and balances the first two empirical moments of the biomarker distribution. At each step, this procedure randomly promotes these goals by minimizing a distance metric between the current allocation and the optimum. In contrast to many of the existing CA procedures, our new proposal allows convergence to any a priori known target allocation, not necessarily balanced. Simulation results are reported in Section 6 and a general discussion and hints for future research concludes the paper (Section 7).

2 Preliminaries

2.1 Notation and Model

Suppose that for each subject entering the trial we observe a quantitative biomarker $Z \in \mathbb{R}$ that is assumed to be a random variable not under the experimenters' control, but it can be measured before assigning a treatment. Subjects come sequentially to the trial and when the ith patient is ready to be enrolled, her/his biomarker value $Z_i = z_i$ can be recorded; then she/he is assigned to the treatment (T)

or to the control (C) according to a given randomization rule, with $\delta_i = 1$ or 0 if the subject is assigned to T or C, respectively, and an outcome Y_i is observed. We assume that $Z_1, Z_2, \ldots$ are independent and identically distributed (iid) random variables with common density function $f(z)$ such that $E(Z_i) = \mu_Z$ and $\text{var}(Z_i) = \sigma_Z^2 < \infty$. Conditionally on the biomarker and the treatments, patients' responses are assumed to be independent, following the linear homoscedastic model

$$Y_i = \delta_i(\mu_T + z_i\beta_T) + (1 - \delta_i)(\mu_C + z_i\beta_C) + \sigma\epsilon_i, \tag{2.1}$$

where the errors ϵ_i are iid standard normal random variables, μ_T and μ_C are the baseline treatment effects, β_T and β_C are possibly different regression parameters, while σ^2 is the common variance.

Under this model, the interaction between the treatments and Z is accounted for, so that patients with different biomarker values may have different responses to the treatments. Thus, the vector $\boldsymbol{\zeta}^t = (\mu_T, \mu_C, \beta_T, \beta_C)$ is of interest since the relative efficacy of the treatments could depend on the values of the biomarker. Indeed, for each value z, the superiority/inferiority of T with respect to C depends on the sign of

$$\theta(z) = E(Y \mid \delta = 1, Z = z) - E(Y \mid \delta = 0, Z = z) = \mu_T - \mu_C + z(\beta_T - \beta_C) = \gamma + z\tau, \tag{2.2}$$

where $\gamma = \mu_T - \mu_C$ is the baseline treatment difference and $\tau = \beta_T - \beta_C$ represents the predictive strength of the biomarker. Clearly τ plays a fundamental role:

- if $\tau = 0$ (i.e., in the absence of treatment/biomarker interactions) then $\theta(z) = \gamma$ for any z; thus, the relative superiority/inferiority of T with respect to C is the same for the whole population and $\beta_T = \beta_C = \beta$ is the common prognostic strength of the biomarker;
- if $\tau \neq 0$, by letting $z^* = -\gamma/\tau$ be the solution of the equation $\theta(z) = 0$, then z^* represents the biomarker threshold defining the subpopulation benefitting from T according to the chosen ethical scenarios.

We assume that larger outcomes are preferable, so that for any patient with $z > z^*$, $\theta(z) > 0$ implies that T is preferable to C, while $\theta(z) < 0$ for those with $z < z^*$, meaning that C should be preferable for this group (obviously, these conditions should be reversed if smaller outcomes are considered better).

Throughout the paper, $\mathbb{I}_n$ denotes the n-dim identity matrix and $\mathbf{1}_n$ is the n-dim vectors of ones. After n assignments, by letting $\mathbf{Y}_n = (Y_1, \ldots, Y_n)^t$, $\mathbf{z}_n = (z_1, \ldots, z_n)^t$ and $\boldsymbol{\delta}_n = (\delta_1, \ldots, \delta_n)^t$, then model (2.1) can be rewritten in matrix form as $\mathbf{Y}_n \sim N\left(\mathbf{X}_n\boldsymbol{\zeta}, \sigma^2\mathbb{I}_n\right)$, where $\mathbf{X}_n = [\boldsymbol{\delta}_n : \mathbf{1}_n - \boldsymbol{\delta}_n : \text{diag}(\boldsymbol{\delta}_n)\mathbf{z}_n : \text{diag}(\mathbf{1}_n - \boldsymbol{\delta}_n)\mathbf{z}_n]$. If $(\mathbf{X}_n^t\mathbf{X}_n)^{-1}$ exists, then the maximum likelihood estimator (MLE) and the least squared estimator of $\boldsymbol{\zeta}$ coincides with $\hat{\boldsymbol{\zeta}}_n = (\hat{\mu}_{Tn}, \hat{\mu}_{Cn}, \hat{\beta}_{Tn}, \hat{\beta}_{Cn})^t = (\mathbf{X}_n^t\mathbf{X}_n)^{-1}\mathbf{X}_n^t\mathbf{Y}_n$ and $\text{var}(\hat{\boldsymbol{\zeta}}_n) = \sigma^2(\mathbf{X}_n^t\mathbf{X}_n)^{-1} = n^{-1}\mathbf{M}_n^{-1}$, where

$$\mathbf{M}_n = \frac{1}{\sigma^2}\begin{pmatrix} \pi & 0 & \pi m_T(z) & 0 \\ 0 & 1-\pi & 0 & (1-\pi)m_C(z) \\ \pi m_T(z) & 0 & \pi m_T(z^2) & 0 \\ 0 & (1-\pi)m_C(z) & 0 & (1-\pi)m_C(z^2) \end{pmatrix} \tag{2.3}$$

is the average information matrix, $\pi = n^{-1}\sum_{i=1}^n \delta_i$ is the proportion allocated to T, $m_T(z) = \boldsymbol{\delta}_n^t\mathbf{z}_n/\boldsymbol{\delta}_n^t\mathbf{1}_n$ and $m_C(z) = (\mathbf{1}_n - \boldsymbol{\delta}_n)^t\mathbf{z}_n/(n - \boldsymbol{\delta}_n^t\mathbf{1}_n)$ represent the biomarker's

empirical means in the two arms. Analogously, $m_T(z^2) = \mathbf{z}_n^t \text{diag}(\boldsymbol{\delta}_n)\mathbf{z}_n / \boldsymbol{\delta}_n^t \mathbf{1}_n$ and $m_C(z^2) = \mathbf{z}_n^t \text{diag}(\mathbf{1}_n - \boldsymbol{\delta}_n)\mathbf{z}_n / (n - \boldsymbol{\delta}_n^t \mathbf{1}_n)$ represent the sample second moments in the two groups. We let $v_j(z) = m_j(z^2) - m_j^2(z)$ be the sample variance of the biomarker in arm j ($j = T, C$).

Within this setting, we propose an enrichment strategy based on two stages that works as follows. The first stage is designed for estimating or testing the predictive strength τ of the biomarker. At the end of the first stage, the null hypothesis $H_0 : \tau = 0$ is tested: if rejected, then there exists a subpopulation benefitting from the treatment T, while if H_0 is not rejected the trial is stopped and the inferential goal lies in the baseline treatment difference γ. More specifically,

- if H_0 is not rejected, then the trial ends and the global superiority of T with respect to C is tested through $H_0' : \gamma \leq 0$ vs $H_1' : \gamma > 0$ (where 0 can be replaced by any specific minimum clinically significant difference elicited by the investigator). If H_0' is not rejected, the trial is stopped for futility (i.e., T can not be considered superior to C), while if H_0' is rejected, the subpopulation benefitting from T coincides with the entire population.
- If H_0 is rejected, the second stage could start in order to estimate the threshold $z^* = -\gamma/\tau$, which identifies the subpopulation of interest. This second stage is designed for optimal inference about the threshold and, at the end of the study, a consistent estimator of z^* is used to define the subpopulation of interest.

Notice that, even if H_0 is rejected at the end of the first stage, the magnitude of the ensuing subpopulation as well as the impact of the enrichment strategy clearly depend on $\Pr(Z > z^*)$, which can be consistently estimated by the corresponding percentage of observed subjects having the biomarker value over the estimated threshold. If this estimate equals 0, it indicates that there is no benefitting subpopulation in practice (and, consistently with the available information about the support of the biomarker, it could be meaningless to continue the study). On the other hand, as this estimate grows a higher percentage of the sample belongs to the estimated subpopulation benefiting from the treatment and so the importance of the enrichment strategy also increases.

3 Optimal allocation for enrichment designs

After n assignments, under model (2.1) classical design criteria are D- and A-optimality, given by $\det \text{var}(\hat{\boldsymbol{\zeta}}_n) = \det\left(n^{-1}\mathbf{M}_n^{-1}\right)$ and $\text{tr}\,\text{var}(\hat{\boldsymbol{\zeta}}_n) = \text{tr}\left(n^{-1}\mathbf{M}_n^{-1}\right)$, respectively. These criteria are particularly useful when the whole parameter vector $\boldsymbol{\zeta}$ is of interest while, due to the role of β_T and β_C, other criteria to be minimized in this setting are:

$$\det \text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) \quad \text{and} \quad \text{tr}\,\text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right), \tag{3.1}$$

which are examples of D_s- and A_s-optimality[29] where only the estimation of the regression coefficients (β_T, β_C) is considered. Moreover, for the peculiarity of enrichment designs other criteria of utmost importance regard inference on the predictive strength τ as well as on the biomarker threshold z^*.

The following theorem

- provides the functional form of the above-mentioned criteria, also showing that $\text{tr}\,\text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) = \text{var}\left(\hat{\tau}_n\right)$;

- shows that a globally balanced design under which the sample means and variances of the biomarker is the same in the two arms is universally optimal for model (2.1) and it is still optimal for the estimation of the biomarker threshold.

Theorem 3.1. *Under model (2.1), the optimality criteria of interest are given by*

$$\begin{aligned}
\det var(\hat{\boldsymbol{\zeta}}_n) &= \left(\frac{\sigma^2}{n}\right)^4 \frac{1}{\pi^2(1-\pi)^2 v_T(z) v_C(z)}, \\
tr\, var(\hat{\boldsymbol{\zeta}}_n) &= \frac{\sigma^2}{n}\left[\frac{1}{\pi(1-\pi)} + \frac{m_T^2(z)+1}{\pi v_T(z)} + \frac{m_C^2(z)+1}{(1-\pi)v_C(z)}\right], \\
\det var\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) &= \left(\frac{\sigma^2}{n}\right)^2 \frac{1}{\pi(1-\pi) v_T(z) v_C(z)}, \\
tr\, var\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) &= var\left(\hat{\tau}_n\right) = \frac{\sigma^2}{n}\left(\frac{1}{\pi v_T(z)} + \frac{1}{(1-\pi)v_C(z)}\right).
\end{aligned}$$

With regard to the estimation of the threshold z^*, by assuming $\tau \neq 0$, the MLE of z^* is $\hat{z}_n^* = -\hat{\gamma}_n/\hat{\tau}_n$ and, via the classical first-order Taylor expansion,

$$var(\hat{z}_n^*) \approx n^{-1}\left(\frac{\sigma}{\tau}\right)^2 \left\{\frac{1}{\pi(1-\pi)} + \frac{\left[m_T(z) + \frac{\gamma}{\tau}\right]^2}{\pi v_T(z)} + \frac{\left[m_C(z) + \frac{\gamma}{\tau}\right]^2}{(1-\pi)v_C(z)}\right\}. \tag{3.2}$$

For every sample size n, an allocation $\boldsymbol{\delta}_n^*$ such that

$$\pi = 1/2 \text{ and } m_T\left(z^i\right) = m_C\left(z^i\right) \text{ for } i = 1, 2 \tag{3.3}$$

is optimal for estimation with respect to any convex criterion $\Phi = \Phi(\mathbf{M}_n)$ which is invariant with respect to the label switching of T and C. Therefore, this design is optimal with respect to all the above-mentioned criteria as well as for estimating the threshold z^*.

Proof. See Appendix A.1.

As previously discussed, in our framework the biomarker is a random variable not under the experimenter's control and, since it is ancillary to the likelihood, inference is conditional on the observed biomarker values. Thus, by letting $m(z) = n^{-1}\mathbf{z}_n^t \mathbf{1}_n$, $m(z^2) = n^{-1}\mathbf{z}_n^t \mathbf{z}_n$ and $v(z) = m(z^2) - m^2(z)$, the (marginal) sample mean $m(z)$ and sample variance $v(z)$ are fixed quantities depending on the enrolled patients; $\boldsymbol{\delta}_n$ is the only component that can be chosen by the experimenter and, given $m(z)$ and $v(z)$, the choice of $\pi, m_T(z)$ and $v_T(z)$ uniquely determines all the elements of $\mathbf{M}_n$, since $m(z) = \pi m_T(z) + (1-\pi)m_C(z)$ and $v(z) = \pi m_T(z^2) + (1-\pi)m_C(z^2) - m^2(z)$, so that

$$v_C(z) = \frac{v(z)}{1-\pi} - \frac{\pi v_T(z)}{1-\pi} - \frac{\pi[m(z) - m_T(z)]^2}{(1-\pi)^2}. \tag{3.4}$$

Thus,

- every convex optimality criterion $\Phi = \Phi(\mathbf{M}_n)$ depends on the design only through the quantities $\pi, m_T(z)$ and $v_T(z)$, that are free to vary;
- the optimal design in (3.3) can be restated as $\pi = 1/2$ and $m_T\left(z^i\right) = m\left(z^i\right)$ for $i = 1, 2$ (namely, $m_T\left(z\right) = m\left(z\right)$ and $v_T\left(z\right) = v\left(z\right)$);
- even if the functional form of some criteria does not depend on the covariate means in the two arms, due to constraint (3.4) the optimal design cannot simply require $\pi = 1/2$ and $v_T(z) = v_C(z)$; indeed in such a case, from (3.4), $v_C(z) = v_T(z) = v(z) - [m(z) - m_T(z)]^2$ achieving its maximum only when $m(z) = m_T(z)$ (i.e., if $m_T(z) = m_C(z)$).

As pointed out in the following remark, in some circumstances the optimal design can be interpreted as a matching of an optimal marginal measure specifying the optimal value of π and an optimal conditional measure that involves the equality of the sample moments of the biomarker in the two arms.

Remark 3.1. *Let* $\mathbf{H} = diag\left(m_T(z), m_C(z)\right)$, $\mathbf{K} = diag\left(m_T(z^2), m_C(z^2)\right)$, $\mathbf{P} = diag(\pi, 1-\pi)$ *be* 2×2 *matrices and let* $\mathbf{Q} = \sigma^{-2} diag\left(\mathbf{P}, \mathbf{P}\right)$ *and* $\mathbf{L} = \begin{pmatrix} \mathbb{I}_2 & \mathbf{H} \\ \mathbf{H} & \mathbf{K} \end{pmatrix}$, *then* $\mathbf{M}_n = \mathbf{QL}$. *It is interesting to notice that the inverse of the average information matrix* $\mathbf{M}_n^{-1}$ *can be factorized as a product of two components:* $\mathbf{L}^{-1}$ *depending on the sample moments of the biomarker in the two arms and* $\mathbf{Q}^{-1}$ *depending on the design only through* π. *Thus, if the optimality criterion is such that* $\Phi(\mathbf{L}^{-1}\mathbf{Q}^{-1}) = \Phi(\mathbf{L}^{-1})\Phi(\mathbf{Q}^{-1})$, *the optimum (3.3) could be view as a design measure* $\xi^*_{\boldsymbol{\delta}|\mathbf{Z}}$ *(conditional on the covariates) which is proportional to the product between*

- *the optimal conditional measure of the biomarker in the two arms* $\xi^*_{\mathbf{Z}|\boldsymbol{\delta}}$, *which specifies the equality of the sample moments in the two groups, and*
- *the optimal marginal measure of the design* $\xi^*_{\boldsymbol{\delta}}$ *giving the weights to* T *and* C *(i.e., the marginal balance due to homoscedasticity).*

For instance, in the case of D-optimality, $\det var(\hat{\boldsymbol{\zeta}}_n) = n^{-4} \det \mathbf{L}^{-1} \det \mathbf{Q}^{-1}$, *where* $\det \mathbf{Q}^{-1} = \sigma^8[\pi(1-\pi)]^{-2}$ *is minimized by* $\pi = 1/2$ *(which is the D-optimal design in the absence of biomarkers, i.e., the optimal marginal measure* $\xi^*_{\boldsymbol{\delta}}$*), while* $\det \mathbf{L}^{-1} = \{v_T(z)v_C(z)\}^{-1}$. *Given* $\pi = 1/2$, *from (3.4) we obtain* $\{v_T(z)v_C(z)\}^{-1} = \{2v_T(z)v(z) - v_T^2(z) - 2v_T(z)[m(z) - m_T(z)]^2\}^{-1}$ *so that the optimum is achieved at* $v(z) - v_T(z) = [m(z) - m_T(z)]^2$, *namely when* $v_T(z) = v_C(z)$ *(which is the optimal conditional measure of the biomarker in the two arms* $\xi^*_{\mathbf{Z}|\boldsymbol{\delta}}$*).*

Notice that this result extends the ones in Atkinson[24], which hold when covariates are under the experimenter's control, to the case of uncontrollable random factors. Moreover, following this reasoning, it is easy to derive optimal designs for more complex models. For instance, by adding in model (2.1) a quadratic term for the biomarker, the information matrix is modified accordingly and the optimal design measure $\xi^*_{\mathbf{Z}|\boldsymbol{\delta}}$ *also involves the equality of the third and fourth moments of the sample distribution of the biomarker in the two arms, leading to the equality of all empirical moments as the model complexity grows.*

While a design satisfying condition (3.3) is optimal under a general class of criteria and it corresponds to the (unique) D-optimal design, other criteria (like, e.g., D_s- and A_s-optimality) could be optimized under weaker conditions, as the following proposition shows.

Proposition 3.1. *Under model (2.1), an allocation vector $\boldsymbol{\delta}_n^*$ such that*

$$m_T(z) = m(z) \text{ and } \pi v_T(z) = v(z)/2 \tag{3.5}$$

is optimal with respect to all the criteria in (3.1).

Proof. See Appendix A.2.

Condition (3.5) is less restrictive than (3.3); indeed, from (3.4), (3.5) could be rewritten as $m_T(z) = m(z)$ and $\pi = v_C(z)/[v_T(z) + v_C(z)]$; therefore given the equality of the biomarker means in the two arms, $\pi = 1/2 \Leftrightarrow v_T(z) = v_C(z) = v(z)$, obtaining condition (3.3).

Remark 3.2. *For estimation of the threshold, criterion (3.2) is minimized by every $\boldsymbol{\delta}_n^*$ such that $\pi = \{1 - [m(z) - m_T(z)]k\}/2$ and*

$$v_T(z) = \frac{2v(z)[m_T(z) + \gamma/\tau]}{(1-k)[m(z) - m_T(z)][m_T + m_C + 2\gamma/\tau]} - \frac{2[m(z) - m_T(z)]^2}{1 + k[m(z) - m_T(z)]},$$

where $k = (m_T + \gamma/\tau)/v_T(z)$. However, excluding the degenerate case $m_T(z) = m_C(z) = m(z)$ leading to condition (3.3), every other optimal allocation depends on the unknown parameters γ and τ, and therefore it can be implemented only through suitably chosen covariate-adjusted response-adaptive (CARA) procedures, as we will discuss in Section 5.

By letting $m(z) = m_T(z) = m_C(z) = 0$ and $v(z) = 1$, Table 1 shows some configurations of the D_s and A_s-optimal design in (3.5) minimizing criteria (3.1).

Table 1. D_s and A_s-optimal design in (3.5).

π	0.10	0.20	0.30	0.40	0.50	0.60	0.70	0.80	0.90
$v_T(z)$	5.00	2.50	1.67	1.25	1.00	0.83	0.71	0.62	0.56
$v_C(z)$	0.56	0.62	0.71	0.83	1.00	1.25	1.67	2.50	5.00

To determine if a subpopulation benefitting from the treatment exists instead of the whole parameter vector $\boldsymbol{\zeta}$, the predictive strength τ of the biomarker plays a crucial role. Since $\hat{\boldsymbol{\zeta}}_n \sim N\left(\boldsymbol{\zeta}, n^{-1}\mathbf{M}_n^{-1}\right)$, then $\sqrt{n}(\hat{\tau}_n - \tau) \sim N(0, \mathbf{c}^t\mathbf{M}_n^{-1}\mathbf{c})$, where $\mathbf{c}^t = (0, 0, 1, -1)$. When σ^2 is a priori known, the statistic

$$W_n = \frac{\sqrt{n}\hat{\tau}_n}{\sigma}\left[\frac{1}{\pi v_T(z)} + \frac{1}{(1-\pi)v_C(z)}\right]^{-1/2}$$

is usually employed for testing the null hypothesis $H_0 : \tau = 0$ versus $H_1 : \tau \neq 0$. Under H_0, W_n^2 is distributed according to a (central) chi-square with 1 degree of freedom. Otherwise, if σ^2 is unknown then it should be consistently estimated by the usual residual sum of squares $\hat{\sigma}_n^2 = (\mathbf{X}_n\hat{\boldsymbol{\zeta}}_n - \mathbf{Y}_n)^t(\mathbf{X}_n\hat{\boldsymbol{\zeta}}_n - \mathbf{Y}_n)/(n-4)$ (in such a case W_n is distributed as a Student-t distribution with $n-4$ degrees of freedom).

Proposition 3.2. *A design $\boldsymbol{\delta}_n^*$ satisfying (3.5) maximizes the power of the test W_n.*

Proof. See Appendix A.3.

3.1 Efficiency

To evaluate the impact of marginal balance and covariate-balance in terms of estimation precision, in this section we compare the performance of the optimal design $\boldsymbol{\delta}_n^*$ in (3.3) with respect to sets of allocations that only partially satisfy conditions (3.3). Starting with the aim of estimating the whole parameter vector $\boldsymbol{\zeta}$, the performances of an allocation $\boldsymbol{\delta}_n$ are first assessed using D- and A-efficiency. Since the minimum values of D- and A-optimality criteria (i.e., evaluated at the optimal design in (3.3)) are

$$\det \operatorname{var}(\hat{\boldsymbol{\zeta}}_n \mid \boldsymbol{\delta}_n^*) = \left(\frac{\sigma^2}{n}\right)^4 \frac{8}{v^2(z)} \quad \text{and} \quad \operatorname{trvar}(\hat{\boldsymbol{\zeta}}_n \mid \boldsymbol{\delta}_n^*) = \frac{4\sigma^2}{n}\left(\frac{m\left(z^2\right)+1}{v(z)}\right),$$

D- and A-efficiencies (namely the relative efficiencies of a generic design compared to the optimal one) are respectively given by

$$\mathcal{E}_D(\boldsymbol{\delta}_n) = \left\{\frac{\det \operatorname{var}(\hat{\boldsymbol{\zeta}}_n \mid \boldsymbol{\delta}_n^*)}{\det \operatorname{var}(\hat{\boldsymbol{\zeta}}_n \mid \boldsymbol{\delta}_n)}\right\}^{1/4} = 2\left[\frac{v_T(z)v_C(z)\pi^2(1-\pi)^2}{v^2(z)}\right]^{1/4}$$

and

$$\mathcal{E}_A(\boldsymbol{\delta}_n) = \frac{\operatorname{trvar}(\hat{\boldsymbol{\zeta}}_n \mid \boldsymbol{\delta}_n^*)}{\operatorname{trvar}(\hat{\boldsymbol{\zeta}}_n \mid \boldsymbol{\delta}_n)} = \frac{4\left(\frac{m\left(z^2\right)+1}{v(z)}\right)}{\frac{m_T(z^2)+1}{\pi v_T(z)} + \frac{m_C(z^2)+1}{(1-\pi)v_C(z)}}.$$

When $\pi = 1/2$, by (3.4) it follows that $v_C(z) = 2v(z) - v_T(z) - 2[m(z) - m_T(z)]^2$; thus, both $\mathcal{E}_D$ and $\mathcal{E}_A$ vanish as the covariate imbalance in the two groups grows. Moreover, if $\pi = 1/2$ and $m_T(z) = m_C(z)$ then $v_C(z) = 2v(z) - v_T(z)$ and both $\mathcal{E}_D$ and $\mathcal{E}_A$ converge to 0 as the ratio $v_T(z)/v(z)$ tends to its extremes values 0 and 2. Whereas, if the design is only covariate-balanced (i.e, $m_T(z) = m_C(z)$ and $v_T(z) = v_C(z)$), then $\mathcal{E}_D = \sqrt{\mathcal{E}_A} = 2\sqrt{\pi(1-\pi)}$, namely the estimation precision could be strongly damaged in the presence of a significant marginal imbalance.

Besides D- and A-efficiency, a measure of efficiency of an allocation $\boldsymbol{\delta}_n$ for the threshold estimation is

$$\mathcal{E}_{z^*}(\boldsymbol{\delta}_n) = \frac{\operatorname{var}(\hat{z}_n^* \mid \boldsymbol{\delta}_n^*)}{\operatorname{var}(\hat{z}_n^* \mid \boldsymbol{\delta}_n)} = \frac{4\left\{1 + \frac{\left[m(z)+\frac{\gamma}{\tau}\right]^2}{v(z)}\right\}}{\frac{1}{\pi(1-\pi)} + \frac{\left[m_T(z)+\frac{\gamma}{\tau}\right]^2}{\pi v_T(z)} + \frac{\left[m_C(z)+\frac{\gamma}{\tau}\right]^2}{(1-\pi)v_C(z)}},$$

which depends also on γ and τ (unlike D- and A-efficiency).

Example 3.1. *Assume an experimental scenario with n patients, in which $m(z) = 0$ and $v(z) = 1$ and we take $\gamma = 0$, corresponding to $z^* = 0$. If $\pi = 1/2$, then $m_C(z) = -m_T(z)$ and $v_C(z) = 2 - v_T(z) - 2m_T^2(z)$; when $m_T(z) = 0.5$ and $v_T(z) = 1.47$ (namely, $m_C(z) = -0.5$ and $v_C(z) = 0.03$), then $\mathcal{E}_D = 0.46$, $\mathcal{E}_A = 0.09$ and $\mathcal{E}_{z^*} = 0.19$ (namely, all the measures of efficiency tend to degenerate as $v_T(z)$ differs from $v_C(z)$). Whereas if the design is only covariate-balanced (i.e, $m_T(z) = m_C(z)$ and $v_T(z) = v_C(z)$), then $\mathcal{E}_{z^*} = \mathcal{E}_A = 4\pi(1-\pi)$, so if $\pi = 0.2$ then $\mathcal{E}_D = 0.8$ and $\mathcal{E}_A = \mathcal{E}_{z^*} = 0.64$. Consider now an allocation such that $\pi = 1/2$ and $m_T(z) = m_C(z)$, if $v_T(z) = 1.95$ and $v_C(z) = 0.05$ then $\mathcal{E}_D = 0.56$ and $\mathcal{E}_A = 0.18$.*

By taking into account the estimation of the regression coefficients (β_T, β_C), the D_s- and A_s-efficiency of a design $\boldsymbol{\delta}_n$ are

$$\mathcal{E}_{D_s}(\boldsymbol{\delta}_n) = \left\{ \frac{\det \text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn} \mid \boldsymbol{\delta}_n^*\right)}{\det \text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn} \mid \boldsymbol{\delta}_n\right)} \right\}^{\frac{1}{2}} = \frac{2\sqrt{\pi(1-\pi)v_T(z)v_C(z)}}{v(z)}$$

and

$$\mathcal{E}_{A_s}(\boldsymbol{\delta}_n) = \frac{\text{trvar}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn} \mid \boldsymbol{\delta}_n^*\right)}{\text{trvar}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn} \mid \boldsymbol{\delta}_n\right)} = \frac{\text{var}\left(\hat{\tau}_n \mid \boldsymbol{\delta}_n^*\right)}{\text{var}\left(\hat{\tau}_n \mid \boldsymbol{\delta}_n\right)} = \frac{4\pi(1-\pi)v_T(z)v_C(z)}{v(z)[\pi v_T(z) + (1-\pi)v_C(z)]}.$$

When $m_T(z) = m_C(z)$, then $v_C(z) = [v(z) - \pi v_T(z)]/(1-\pi)$ and therefore $\mathcal{E}_{D_s} = \sqrt{\mathcal{E}_{A_s}} = 2v(z)^{-1}\sqrt{\pi v_T(z)[v(z) - \pi v_T(z)]}$, which decreases as $v_T(z)/v(z)$ tends to be different from 1.

Example 3.2. *Consider a clinical trial with n patients in which $m(z) = 0$ and $v(z) = 1$. Table 2-3 show D_s- and A_s-efficiency when $m_T(z) = m_C(z)$ (by fixing $v_T(z) = 0.1$) and when $\pi v_T(z) = v(z)/2$ (by setting $m_T(z) = 0.4$), respectively.*

Table 2. D_s- and A_s-efficiency when $m_T(z) = m_C(z)$.

π	$m_T(z)$	$m_C(z)$	$v_T(z)$	$v_C(z)$	$\mathcal{E}_{D_s}$	$\mathcal{E}_{A_s}$
0.20	0	0	0.10	1.23	0.28	0.08
0.50	0	0	0.10	1.90	0.44	0.19
0.80	0	0	0.10	4.60	0.57	0.29

Table 3. D_s- and A_s-efficiency when $\pi v_T(z) = v(z)/2$.

π	$m_T(z)$	$m_C(z)$	$v_T(z)$	$v_C(z)$	$\mathcal{E}_{D_s}$	$\mathcal{E}_{A_s}$
0.20	0.40	-0.10	0.10	1.18	0.27	0.08
0.50	0.40	-0.40	0.25	1.43	0.60	0.43
0.80	0.40	-1.60	0.40	0.20	0.23	0.14

4 Optimal designs under heteroscedasticity

To generalize the previous results for possible heteroscedasticity of the two arms assume now that, conditionally on the biomarker and the treatments, patient responses are normally independent outcomes following

$$Y_i = \delta_i(\mu_T + z_i\beta_T + \sigma_T\epsilon_i) + (1-\delta_i)\left(\mu_C + z_i\beta_C + \sigma_C\epsilon_i\right), \tag{4.1}$$

where σ_T^2 and σ_C^2 are the variances of the responses in the two arms. Let $\boldsymbol{\Sigma}_n = \text{diag}\left(\delta_i\sigma_T^2 + (1-\delta_i)\sigma_C^2\right)_{i=1,\ldots,n}$, if $(\mathbf{X}_n^t\boldsymbol{\Sigma}_n^{-1}\mathbf{X}_n)^{-1}$ exists then the estimator of the regression coefficient now becomes $\hat{\boldsymbol{\zeta}}_n = (\mathbf{X}_n^t\boldsymbol{\Sigma}_n^{-1}\mathbf{X}_n)^{-1}\mathbf{X}_n^t\boldsymbol{\Sigma}_n^{-1}\mathbf{Y}_n$ with $\text{var}(\hat{\boldsymbol{\zeta}}_n) = (\mathbf{X}_n^t\boldsymbol{\Sigma}_n^{-1}\mathbf{X}_n)^{-1} = n^{-1}\tilde{\mathbf{M}}_n^{-1}$, where $\tilde{\mathbf{M}}_n = \sigma^2\text{diag}(\mathbf{S},\mathbf{S})\mathbf{M}_n$ and $\mathbf{S} = \text{diag}(\sigma_T^{-2};\sigma_C^{-2})$.

In this setting, the optimality criteria discussed in Section 3 can be directly obtained by simply replacing $\mathbf{M}_n$ with $\tilde{\mathbf{M}}_n$. Regardless of the heteroscedasticity, as shown in the following theorem the D and D_s-optimal designs are still the same as in the homoscedastic case; whereas, for A, A_s-optimality and the estimation of the biomarker threshold, the optimal design combines Neyman allocation $\pi_N = \sigma_T/(\sigma_T + \sigma_C)$ as marginal target with suitable covariate-balance conditions.

Theorem 4.1. *Under model (4.1), the criteria for D and A-optimality become, respectively,*

$$\det var(\hat{\boldsymbol{\zeta}}_n) = \frac{\sigma_T^4 \sigma_C^4}{n^4 \pi^2 (1-\pi)^2 v_T(z) v_C(z)},$$

$$tr\, var(\hat{\boldsymbol{\zeta}}_n) = \frac{\sigma_T^2}{\pi} + \frac{\sigma_C^2}{1-\pi} + \frac{\sigma_T^2}{\pi}\left(\frac{m_T^2(z)+1}{v_T(z)}\right) + \frac{\sigma_C^2}{(1-\pi)}\left(\frac{m_C^2(z)+1}{v_C(z)}\right).$$

Moreover,

$$\det var\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) = \frac{\sigma_T^2 \sigma_C^2}{n^2 \pi (1-\pi) v_T(z) v_C(z)}, \tag{4.2}$$

$$tr\, var\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) = var\left(\hat{\tau}_n\right) = \frac{1}{n}\left\{\frac{\sigma_T^2}{\pi v_T(z)} + \frac{\sigma_C^2}{(1-\pi) v_C(z)}\right\} \tag{4.3}$$

and

$$var(\hat{z}_n^*) \approx n^{-1}\left(\frac{1}{\tau}\right)^2 \left[\frac{\sigma_T^2}{\pi} + \frac{\sigma_C^2}{1-\pi} + \frac{\sigma_T^2\left[m_T(z) + \frac{\gamma}{\tau}\right]^2}{\pi v_T(z)} + \frac{\sigma_C^2\left[m_C(z) + \frac{\gamma}{\tau}\right]^2}{(1-\pi) v_C(z)}\right]. \tag{4.4}$$

For any n, $\boldsymbol{\delta}_n^*$ satisfying (3.3) is still D-optimal, while the A-optimal design satisfies

$$\pi = \pi_N \quad \text{and} \quad m_T\left(z^i\right) = m_C\left(z^i\right) \ \text{ for } i = 1, 2, \tag{4.5}$$

which also optimizes the estimation of the biomarker threshold $\hat{z}^*$. Furthermore, $\boldsymbol{\delta}_n^*$ satisfying (3.5) optimizes criterion (4.2), while every allocation such that

$$m_T(z) = m_C(z) \quad \text{and} \quad \pi v_T(z) = \pi_N v(z) \tag{4.6}$$

minimizes (4.3) and also maximizes the power of the corresponding Wald test.

Proof. See Appendix A.4.

Therefore, the design is both A- and A_s-optimal, it minimizes the variance of the estimated threshold and also maximizes the power of the Wald test. Clearly, when $\sigma_T^2 = \sigma_C^2$ condition (4.5) coincides with (3.3). The relative efficiency of allocation (3.3) with respect to the optimal design (4.5) under heteroscedasticity is $\mathcal{E}_{A_s} = \mathcal{E}_A = \mathcal{E}_{z^*} = (\sigma_T + \sigma_C)^2/2(\sigma_T^2 + \sigma_C^2)$, showing that the measures of estimation efficiency reach the maximum when $\sigma_T/\sigma_C = 1$, while they drastically decrease as σ_T and σ_C tend to differ; notice that the loss of efficiency is always lower than 0.5 (that represents the limiting scenario under which the ratio σ_T/σ_C goes to 0 or to $+\infty$). Thus, the estimation precision could be extremely affected when balanced allocation is used as in standard practice, even if the covariate balance is achieved.

The optimal allocations derived in this paper, in both the homoscedastic and heteroscedastic set-up, are summarized in Table 4.

Table 4. Optimal designs: summary. Condition II is weaker than I and condition IV is weaker than III.

I	$\pi = 1/2$	$m_T(z) = m_C(z)$	$v_T(z) = v_C(z)$	(3.3)
II		$m_T(z) = m_C(z)$	$\pi v_T(z) = v(z)/2$	(3.5)
III	$\pi = \pi_N$	$m_T(z) = m_C(z)$	$v_T(z) = v_C(z)$	(4.5)
IV		$m_T(z) = m_C(z)$	$\pi v_T(z) = \pi_N v(z)$	(4.6)

Objective		Criterion	Homoscedasticity	Heteroscedasticity
Estimation	ζ	D	I	I
		A	I	III
	β_T, β_C	D_s	II (I)	II (I)
		A_s	II (I)	IV (III)
	z^*	var$(\hat{z}^*)$	I	III
Testing	$\beta_T - \beta_C = 0$	power	II (I)	IV (III)

5 A new covariate-adaptive randomization procedure

As shown in Theorems 3.1 and 4.1, the optimal designs satisfying (3.3) and (4.5) could be considered the benchmark for models (2.1) and (4.1), because they guarantee optimality with respect to all the above-mentioned criteria (see also Table 4). However, such designs cannot be achieved (in general) for any sample size, since the biomarker is not under the experimenter's control, but they could be implemented sequentially by forcing at each step the treatment assignment to approach the optimal asymptotically. In what follows we introduce a new CA randomization procedure aimed at achieving a high-order convergence to a desired optimal design of the form

$$\pi = \pi^*, \quad m_T(z) = m(z) \text{ and } v_T(z) = v(z), \tag{5.1}$$

where the marginal optimal target π^* is assumed to be a priori known. This clearly covers the optimal design in (3.3) and also the one in (4.5) provided that the treatment variances are a priori known.

The key idea is to formalize at each step the performance of the design (in terms of its actual allocation) as a point in an ideal space where each axis corresponds to a specific dimension related to the involved constraints of the optimum. In this setting, the Euclidean norm of this vector is a measure of the distance between the actual design and the optimum (i.e., the origin), which will be sequentially minimized by forcing its reduction probabilistically.

With regard to the notation, due to the sequential evolution of the procedure, from now on we set $\pi = \pi_n$, $m_T(z) = m_{Tn}(z)$, $m_T(z^2) = m_{Tn}(z^2)$, $m(z) = m_n(z)$ and $m\left(z^2\right) = m_n\left(z^2\right)$, to stress that these quantities are evaluated at step n. Let us define $\mathbb{Z}_n = [\mathbf{1}_n, \mathbf{z}_n, \text{diag}(\mathbf{z}_n)\mathbf{z}_n]$, $\mathbf{r}_n = (1, z_n, z_n^2)^t$ and

$$\mathbf{u}_n^t = \left(\boldsymbol{\delta}_n - \mathbf{1}_n \pi^*\right)^t \mathbb{Z}_n = n\left(\pi_n - \pi^*, \pi_n m_{Tn}(z) - \pi^* m_n(z), \pi_n m_{Tn}\left(z^2\right) - \pi^* m_n\left(z^2\right)\right).$$

If $\mathbf{u}_n = (0,0,0)^t$ the corresponding allocation attains its optimal value, so the procedure works on sequentially minimizing the squared Euclidean norm $\|\mathbf{u}_n\|^2 = \mathbf{u}_n^t \mathbf{u}_n$.

When the $(n+1)$th subject with biomarker z_{n+1} joins the study, (s)he can be assigned to T or C and we can compute the corresponding imbalances:

- if $\delta_{n+1}=1$ then $\mathbf{u}_{n+1|T}=\mathbf{u}_n+(1-\pi^*)\mathbf{r}_{n+1}$ while
- if $\delta_{n+1}=0$ then $\mathbf{u}_{n+1|C}=\mathbf{u}_n-\pi^*\mathbf{r}_{n+1}$;

thus $\|\mathbf{u}_{n+1|T}\|^2-\|\mathbf{u}_{n+1|C}\|^2=\mathbf{r}_{n+1}^t\left[2\mathbf{u}_n+(1-2\pi^*)\mathbf{r}_{n+1}\right]$ and therefore (s)he is randomly forced to the treatment minimizing this difference by letting $\Pr(\delta_{n+1}=1\mid\boldsymbol{\delta}_n,\mathbf{z}_{n+1})=h\left(\mathbf{r}_{n+1}^t\left[2\mathbf{u}_n+(1-2\pi^*)\mathbf{r}_{n+1}\right]\right)$, where

$$h(x)=\begin{cases}\pi^*+\varepsilon, & \text{if } x<0\\ \pi^*, & \text{if } x=0,\\ \pi^*-\varepsilon, & \text{if } x>0\end{cases}\qquad 0<\varepsilon<\min\{\pi^*;1-\pi^*\}. \tag{5.2}$$

Theorem 5.1. *Under the proposed sequential procedure, $\{\mathbf{u}_n\}_{n\in\mathbb{N}}$ is a Markov chain on $\mathbb{R}^3$ with $\mathbf{u}_0=(0,0,0)^t$ and $\mathbf{u}_{n+1}=\mathbf{u}_n+(\delta_{n+1}-\pi^*)\mathbf{r}_{n+1}$ a.s. for every n. Moreover, $\{\mathbf{u}_n\}_{n\in\mathbb{N}}$ is bounded in probability with $\mathbf{u}_n=O_p(1)$; therefore, as $n\to\infty$, $\pi_n\to\pi^*$, $m_{Tn}(z)-m_{Cn}(z)\to 0$ and $m_{Tn}\left(z^2\right)-m_{Cn}\left(z^2\right)\to 0$ in probability.*

Proof. See Appendix A.5.

When $\pi^*=1/2$, the proposed procedure corresponds to the Efficient Covariate-Adaptive Design[30] which randomly assigns the subjects to the treatments via Efron's allocation function[31] in order to converge to (3.3). Whereas, in the absence of biomarker $\mathbb{Z}_n=\mathbf{1}_n$ and $\mathbf{r}_n=1$ for every n, so $\mathbf{u}_n=n(\pi_n-\pi^*)$. Thus, from (5.2), our proposal becomes a restricted randomization rule such that $\Pr(\delta_{n+1}=1\mid\boldsymbol{\delta}_n)=h\left(2n(\pi_n-\pi^*)+(1-2\pi^*)\right)$. This clearly generalizes Efron's biased coin design (BCD) to the case of an a priori known target π^* not necessarily balanced, also guaranteeing the same order of convergence.

Remark 5.1. *With respect to the design in (4.5), in the case of unknown treatment variances, as well as for some less restrictive optimal conditions like, e.g., (4.6) and those of Remark 3.2, all these optimal designs depend on the unknown model parameters and therefore they cannot be approached asymptotically via CA procedures. These designs could be targeted by suitably chosen CARA procedures that estimate at each step the unknown model parameters and then redirect the allocations towards the optimum[32]. However, due to the use of the outcomes for estimation purposes, these procedures are characterized by a slower convergence with respect to the proposed CA randomization.*

6 Simulation results

This section is dedicated to the study of the behavior of the suggested CA procedure, referred to as sequential efficient design (SED) in what follows, that aims at converging either to the optimal design in (3.3) or in (4.5), namely to the allocations in I and III of Table 4. For the sake of comparison, we consider CA procedures developed for balancing the allocation across continuous covariates, namely

- Atkinson's[23] optimal BCD (ATK), which sequentially minimizes the loss of estimation efficiency;

- the CA randomization procedure proposed by Ma and Hu[33] (MH), which minimizes the distance between the covariate densities in the treatment groups (with biasing probability equal to 0.8).

Moreover, for the homoscedastic scenario, we include the permuted block design with block size 4 (PBD) intending to balance the two treatments, while in the the heteroscedastic set-up we consider the PBD with block size b aimed at achieving Neyman allocation π_N within each block (PBD$_{b,N}$). Note that complete randomization was also included in the simulations but has been omitted from the tables and figures, as the results were inferior to those of the permuted block design. All trials have been simulated 20000 times assuming standard normal biomarker distribution. The first stage has the aim of estimating/testing τ and, if $\tau = 0$ is rejected, a second stage is performed with the aim of estimating the biomarker threshold. A shiny web app to implement the sequential efficient design is available at https://rfrieri.shinyapps.io/SequentialEfficientDesignApp/.

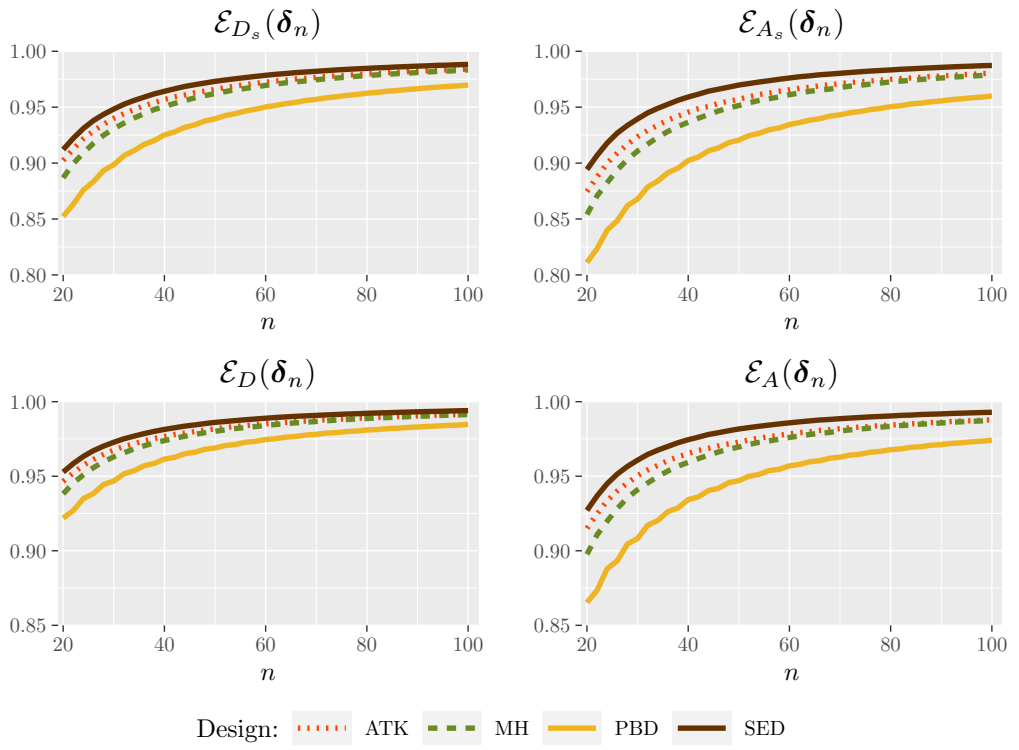
6.1 Estimation efficiency and power of stage 1

The measures of estimation efficiency ($\mathcal{E}_{D_s}$ and $\mathcal{E}_{A_s}$ for the regression coefficients and $\mathcal{E}_D$ and $\mathcal{E}_A$ for $\boldsymbol{\zeta}$) do not depend on γ and τ so we set $\gamma = 0$ and $\tau = 1$ in this study. In the homoscedastic case (where $\sigma = 1$ is assumed), $\pi^* = 1/2$ and we set $\varepsilon = 0.3$ for SED. Figure 1 reports the behavior of the efficiencies with n varying between 20 and 100. The SED is superior to all the competitors, especially for small sample sizes and when A-optimality is of interest.

The results of the same study for the heteroscedastic case with $\sigma_T = 3$ and $\sigma_C = 1$ are displayed in Figure 2. Since the D- and D_s- optimal allocations are such that $\pi^* = 0.5$ (Theorem 4.1), the SED is gauged to achieve this target with $\varepsilon = 0.3$. To target the A- and A_s- optimal designs, the SED was instead implemented with $\pi^* = \pi_N = 3/4$ and $\varepsilon = 0.15$. In terms of D_s- and D- optimality, the PBD is associated with the lowest estimation efficiency. Instead, our proposal attains larger values of $\mathcal{E}_{A_s}$ and $\mathcal{E}_A$ with respect to ATK and MH procedures for which the efficiency is below 0.8; PBD$_{4,N}$ performs quite well but it is still dominated by SED.

To analyze the performances of the above-mentioned procedures in terms of power at the end of stage 1, we set $\beta_C = 0.2$, $\beta_T = 0.8, 1, 1.2, 1.4$, $\mu_T = \mu_C = 1$, and $\alpha = 0.05$. Table 5 shows the simulated average power of the test W_n, denoted by $\mathcal{P}(\boldsymbol{\delta}_n)$. For the homoscedastic case (with $\sigma = 1$), $\pi^* = 0.5$ and we set and $\varepsilon = 0.3$. Under heteroscedasticity, we set $\sigma_C = 1$ and $\sigma_T = 2, 3, 4$, so that $\pi^* = \pi_N = 0.67, 0.75, 0.8$ and $\varepsilon = 0.15$. Table 5 shows that for a fixed value of β_T, the higher σ_T is, the higher the required sample size becomes to achieve similar values of the power. For homoscedastic responses, the three CA randomization procedures strongly outperform the PBD in terms of power, with $\mathcal{P}(\boldsymbol{\delta}_n)$ that tends to assume similar values as β_T gets closer to β_C. Under heteroscedasticity, in some experimental settings, the gain of power in adopting the SED is over the 10% with respect to ATK and MH that seem to be inadequate for hypothesis testing in the heteroscedastic set-up. The power induced by the PBD$_{b,N}$ reaches higher values and, especially for higher σ_T/larger sample sizes, the values are similar to the ones obtained with our procedure. However, as is well-known, under the PBD$_{b,N}$ the allocation could be highly predictable. For instance, if $b = 4$ and $\pi_N = 3/4$, if the first patient of the block is assigned to C the next three assignments to complete the block will be completely deterministic. The lack of randomness in the assignments leaves the experimental procedure open to selection bias, that could affect the validity of the trial's analysis and results[28,31].

Figure 1. D_s- and A_s-efficiency for the estimation of the regression coefficients (β_T, β_C), ($\mathcal{E}_{D_s}$ and $\mathcal{E}_{A_s}$) and D- and A- efficiency for the estimation of $\boldsymbol{\zeta}$, ($\mathcal{E}_D$ and $\mathcal{E}_A$) with $\sigma = 1$. SED is performed with $\pi^* = 1/2$ and $\varepsilon = 0.3$.



6.2 *Estimation efficiency for the threshold at stage 2*

After stage 1, an independent stage 2 is carried out to estimate the threshold. In Table 6 we set $\sigma_C = 1$, $\beta_C = 0.2$ and $\beta_T = 1.4, 1.2, 1, 0.8$; for each experimental scenario we consider three possible choices of the μ's: $\mu_T = 1.4$ and $\mu_C = 1$, $\mu_T = \mu_C = 1$ and, finally, $\mu_T = 1$ and $\mu_C = 1.4$, leading to different values of z^* (reported in the table). For SED we set $\varepsilon = 0.3$ in the homoscedastic case, while when $\sigma_T = 2, 3, 4$, then $\pi^* = \pi_N = 0.67, 0.75, 0.8$ and we set $\varepsilon = 0.15$. For decreasing β_T, the threshold tends to assume more extreme values (when $\gamma \neq 0$). In the homoscedastic set-up, the empirical variance of the estimated threshold is very similar across the CA procedures and the PBD. However, it should be considered that the SED is superior in terms of estimation efficiency (see Figures 1 and 2). The case of heterogeneous responses underlines the advantages of adopting the proposed CA design, which is associated with smaller var$(\hat{z}_n^*)$ and the gain drastically increases as σ_T differs from σ_C. The PBD$_{b,N}$ is the procedure that presents values of the simulated average variance smaller with respect to those achieved under ATK and MH.

Figure 2. D_s- and A_s-efficiency for the estimation of the regression coefficients (β_T, β_C), ($\mathcal{E}_{D_s}$ and $\mathcal{E}_{A_s}$) and D- and A-efficiency for the estimation of $\boldsymbol{\zeta}$, ($\mathcal{E}_D$ and $\mathcal{E}_A$), with $\sigma_T = 3$, $\sigma_C = 1$. To target the D and D_s-optimal designs the SED has been implemented with $\pi^* = 1/2$ and $\varepsilon = 0.3$; to target the A and A_s- optimal designs the SED has been implemented with $\pi^* = \pi_N = 3/4$ and $\varepsilon = 0.15$.

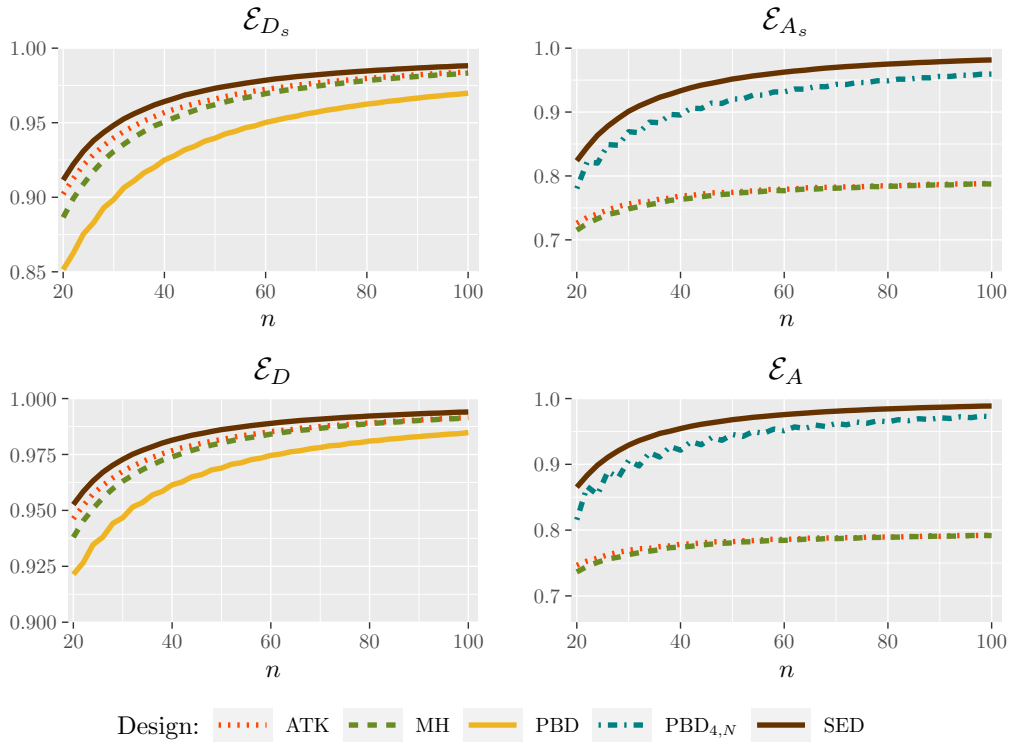


Figure 3 displays the efficiency in the threshold estimation $\mathcal{E}_{z^*}$ which depends on γ/τ: by setting $\gamma = 0$ then $z^* = 0$ regardless of τ. The results are consistent with those previously obtained and similar considerations hold: while for the homoscedastic case the CA randomization procedures guarantee very high efficiency, under heteroscedasticity $\mathcal{E}_{z^*}(\boldsymbol{\delta}_n) < 0.8$ for all the designs aside from the SED and the PBD$_{4,N}$.

Table 5. Stage 1: Power $\mathcal{P}(\boldsymbol{\delta}_n)$ with $\alpha = 0.05$ and $\beta_C = 0.2$. With regard to SED, in the homoscedastic case ($\sigma = 1$) we set $\varepsilon = 0.3$, while in the remaining scenarios ($\sigma_C = 1$ and $\sigma_T = 2, 3, 4$) we set $\varepsilon = 0.15$.

		$\beta_T = 1.4$	$\beta_T = 1.2$	$\beta_T = 1$	$\beta_T = 0.8$
	n	25	50	75	100
$\sigma = 1$	PBD	0.761	0.906	0.766	0.530
	SED	0.796	0.920	0.783	0.554
	ATK	0.785	0.918	0.782	0.535
	MH	0.777	0.916	0.778	0.540
	n	50	75	100	125
$\sigma_T = 2$	$\text{PBD}_{3,N}$	0.762	0.795	0.733	0.593
	SED	0.778	0.801	0.746	0.599
	ATK	0.743	0.766	0.704	0.556
	MH	0.737	0.754	0.698	0.559
	n	100	125	175	200
$\sigma_T = 3$	$\text{PBD}_{4,N}$	0.829	0.780	0.734	0.553
	SED	0.837	0.786	0.751	0.555
	ATK	0.755	0.693	0.652	0.473
	MH	0.754	0.692	0.656	0.469
	n	150	200	250	350
$\sigma_T = 4$	$\text{PBD}_{5,N}$	0.823	0.792	0.707	0.613
	SED	0.830	0.800	0.713	0.619
	ATK	0.706	0.678	0.581	0.487
	MH	0.679	0.673	0.577	0.487

Figure 3. Efficiency in terms of threshold estimation ($\mathcal{E}_{z^*}$) when $\gamma = 0$. For the homoscedastic model, $\sigma = 1$, $\pi^* = 1/2$ and $\varepsilon = 0.3$; for the heteroscedastic model $\sigma_T = 3$, $\sigma_C = 1$, $\pi^* = \pi_N = 3/4$ and $\varepsilon = 0.15$.

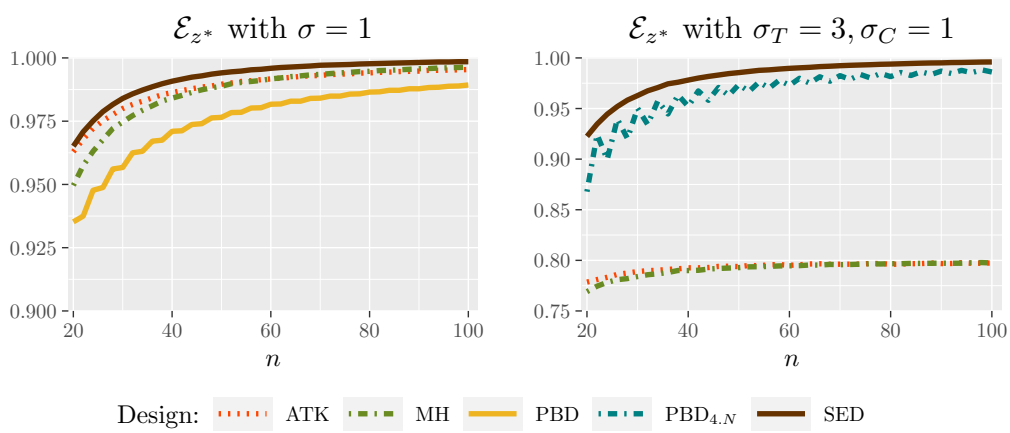


Table 6. Stage 2: var$(\hat{z}_n^*)$ with $\beta_C = 0.2$. With regard to SED, in the homoscedastic case ($\sigma = 1$) we set $\varepsilon = 0.3$, while in the remaining scenarios ($\sigma_C = 1$ and $\sigma_T = 2, 3, 4$) we set $\varepsilon = 0.15$.

	Design		$\beta_T = 1.4$			$\beta_T = 1.2$			$\beta_T = 1$		
		z^*	-0.33	0	0.33	-0.4	0	0.4	-0.5	0	0.5
		n		40			50			75	
$\sigma = 1$	PBD	var$(\hat{z}_n^*)$	0.109	0.099	0.111	0.131	0.134	0.129	0.144	0.122	0.144
	SED	var$(\hat{z}_n^*)$	0.106	0.096	0.103	0.125	0.127	0.125	0.141	0.120	0.142
	ATK	var$(\hat{z}_n^*)$	0.107	0.099	0.107	0.127	0.130	0.126	0.142	0.122	0.146
	MH	var$(\hat{z}_n^*)$	0.108	0.099	0.106	0.126	0.128	0.128	0.145	0.121	0.147
		n		45			55			80	
$\sigma_T = 2$	$\text{PBD}_{3,N}$	var$(\hat{z}_n^*)$	0.234	0.228	0.225	0.267	0.264	0.274	0.292	0.297	0.300
	SED	var$(\hat{z}_n^*)$	0.221	0.220	0.219	0.267	0.261	0.271	0.286	0.289	0.287
	ATK	var$(\hat{z}_n^*)$	0.244	0.249	0.247	0.283	0.291	0.293	0.315	0.327	0.320
	MH	var$(\hat{z}_n^*)$	0.250	0.248	0.255	0.290	0.298	0.287	0.316	0.327	0.320
		n		75			85			95	
$\sigma_T = 3$	$\text{PBD}_{4,N}$	var$(\hat{z}_n^*)$	0.250	0.253	0.258	0.316	0.330	0.315	0.424	0.435	0.428
	SED	var$(\hat{z}_n^*)$	0.249	0.245	0.248	0.309	0.316	0.312	0.417	0.426	0.415
	ATK	var$(\hat{z}_n^*)$	0.307	0.308	0.301	0.377	0.387	0.371	0.491	0.506	0.492
	MH	var$(\hat{z}_n^*)$	0.305	0.301	0.308	0.374	0.383	0.370	0.492	0.503	0.488
		n		75			90			100	
$\sigma_T = 4$	$\text{PBD}_{5,N}$	var$(\hat{z}_n^*)$	0.377	0.387	0.381	0.442	0.434	0.443	0.564	0.576	0.575
	SED	var$(\hat{z}_n^*)$	0.376	0.373	0.370	0.431	0.430	0.436	0.533	0.553	0.551
	ATK	var$(\hat{z}_n^*)$	0.466	0.480	0.473	0.541	0.538	0.563	0.650	0.647	0.662
	MH	var$(\hat{z}_n^*)$	0.462	0.476	0.472	0.539	0.550	0.529	0.666	0.672	0.661

7 Discussion

With the advent of precision medicine, the determination of certain candidate biomarkers has prompted research in enrichment designs. However, the optimal design problem for enrichment trial has received little attention and most of the existing proposals adopt balanced allocation among the treatment groups and deal with dichotomous markers[6]. Instead, when the biomarker is defined on a continuous scale, a threshold to discriminate the benefitting subpopulation has to be estimated. Optimal allocations for inference on the threshold are provided in this paper. The biomarker is accounted for as a random variable and, since it is ancillary to the likelihood, inference is conditional on its observed values. The optimal design problem for the estimation of a threshold to identify the benefitting subpopulation is innovative and it is different from others because the experimenter cannot directly control the biomarker values of future enrolled patients.

Analytic and numerical results demonstrate a remarkable gain in terms of estimation efficiency of model parameters and threshold of a continuous biomarker when the optimal allocation is implemented via the proposed covariate-adaptive randomization, especially in the case of heterogeneous responses and for smaller sample sizes. As far as power and variance of the estimated threshold are concerned, the proposed design as well as other covariate-adaptive procedures guarantee good performance compared to the permuted block design in the homoscedastic set-up. Whereas, under deviations from this setting, our new covariate-adaptive randomization outperforms other designs: its use becomes extremely important to carry out an efficient clinical trial under heteroscedasticity, as our procedure allows targeting unequal allocation, at the same time balancing over the first two empirical moments of the biomarker's distribution.

The simulation study also demonstrates that, for estimating the threshold accurately, a moderate number of patients is required to be enrolled in the trial. Usually, these preliminary studies are performed on a tiny sample but, since the estimated threshold is defined to be employed for future clinical experiments and drug use, an adequate sample size should be achieved [17] and the proposed randomization allows maximizing efficiency of the study. Important parameters that have been found to affect the design of enrichment trials are the variance of the outcome and the biomarker prevalence in the benefitting subgroup. Within our setting, the impact of the enrichment strategy can be assessed by the sample proportion of patients with biomarker values above the threshold; values close to 0 or 1 lead to the question of whether or not is worth enriching, depending on the gravity/rarity of the disease and/or cost of evaluating the biomarker, and/or side effects of the treatment[6,16,17].

Note that the optimal design for the heteroscedastic model requires prior knowledge of the ratio of the outcome variances in both treatments. However, variances are rarely known in designing any clinical trial, and in practice, we make a best guess based on the literature or the investigator's knowledge, and this is what we use in sample size computations. We often investigate the change in sample size or power if our best guess is wrong, and this traditional method of sample size computation applies here as well. From a design perspective, optimal designs in the heteroscedastic case will depend directly on the variances, and initially these can be a best guess from the literature or a preliminary study, and Neyman allocation would be a ratio of the guessed standard deviations. Adaptive designs, as mentioned in Remark 5.1, can adaptively update these guesses using the sequentially accrued data.

The issue of deriving the optimal sample size for a two-stage enrichment trial has been addressed by Frieri et al. [17] in a related context. The analog of their approach to the one adopted in this paper would be to find the sample size that guarantees a desired power in testing whether a benefitting

subpopulation exists for stage 1 (i.e., the minimum n guaranteeing a given simulated average power of the test $H_0 : \tau = 0$ vs $H_0 : \tau \neq 0$) and that bounds the variance of the estimated threshold for stage 2 (i.e., the minimum n for which var$(\hat{z}^*)$ is less than a desired upper bound, for instance via (4.4)). Another possible approach in the case of heteroscedasticity for sample size selection could be a maximin strategy[34,35]. For instance, given a fixed total variance $\sigma_T^2 + \sigma_C^2$, the experimenter could derive σ_T^2/σ_C^2 that maximizes var$(\hat{\tau}_n)$ within a plausible range of variance ratios. Then, given this choice, the optimal design could be selected by minimizing the variance of $\hat{\tau}_n$, guaranteeing a power level at the smallest sample size.

In the case of more complex models, drawing design considerations becomes more complicated. For instance, the optimal allocation for estimating the threshold in a generalized linear models is still unknown. Further work aimed at filling this gap would be particularly useful to promote an efficient implementation of enrichment trials and to support precision medicine. Another useful extension for a more accurate identification of the benefitting subpopulation, would be to derive the optimal design when many predictive biomarkers (continuous and/or categorical) are included in the model, with potential interactions among them.

Acknowledgements

The authors of this paper wish to thank the Editor and the referees, who made substantial comments that improved the paper. Alessandro Baldi Antognini, Rosamarie Frieri and Maroussa Zagoraiou were supported by EU funding within the NextGenerationEU PRIN 2022 "Optimal and adaptive designs for modern medical experimentation" (2022TRB44L). Alessandro Baldi Antognini was also supported by EU funding within the NextGenerationEU-MUR PNRR Extended Partnership initiative on Emerging Infectious Diseases (Project no. PE00000007, INF-ACT).

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A Appendix

A.1 Proof of Theorem 3.1

We firstly derive the expressions for the considered optimality criteria. Recalling that $\mathbf{H} = \text{diag}\,(m_T(z), m_C(z))$, $\mathbf{K} = \text{diag}\left(m_T(z^2), m_C(z^2)\right)$, $\mathbf{P} = \text{diag}(\pi, 1-\pi)$, $\mathbf{Q} = \sigma^{-2}\text{diag}\,(\mathbf{P}, \mathbf{P})$ and $\mathbf{L} = \begin{pmatrix} \mathbb{I}_2 & \mathbf{H} \\ \mathbf{H} & \mathbf{K} \end{pmatrix}$. Let us also define $\mathbf{V} = \text{diag}\,(v_T(z), v_C(z)) = \mathbf{K} - \mathbf{H}^2$, then

$$\mathbf{M}_n^{-1} = \mathbf{L}^{-1}\mathbf{Q}^{-1} = \left(\begin{array}{c|c} \mathbf{V^{-1}KP^{-1}} & -\mathbf{V^{-1}HP^{-1}} \\ \hline -\mathbf{V^{-1}HP^{-1}} & \mathbf{V^{-1}P^{-1}} \end{array}\right)$$

where

$$\mathbf{L}^{-1} = \begin{pmatrix} \frac{m_T(z^2)}{v_T(z)} & 0 & -\frac{m_T(z)}{v_T(z)} & 0 \\ 0 & \frac{m_C(z^2)}{v_C(z)} & 0 & -\frac{m_C(z)}{v_C(z)} \\ -\frac{m_T(z)}{v_T(z)} & 0 & \frac{1}{v_T(z)} & 0 \\ 0 & -\frac{m_C(z)}{v_C(z)} & 0 & \frac{1}{v_C(z)} \end{pmatrix} \quad \text{and} \quad \mathbf{V^{-1}P^{-1}} = \sigma^2 \begin{pmatrix} \frac{1}{\pi v_T(z)} & 0 \\ 0 & \frac{1}{(1-\pi)v_C(z)} \end{pmatrix}.$$

Therefore $\det \text{var}(\hat{\boldsymbol{\zeta}}_n) = n^{-4} \det \mathbf{L}^{-1} \det \mathbf{Q}^{-1}$, where $\det \mathbf{Q}^{-1} = \sigma^8[\pi(1-\pi)]^{-2}$ and $\det \mathbf{L}^{-1} = (\det \mathbf{V})^{-2} \det(\mathbf{K} - \mathbf{H}^2) = (\det \mathbf{V})^{-1} = [v_T(z)v_C(z)]^{-1}$.
Moreover, $\text{tr}\,\text{var}(\hat{\boldsymbol{\zeta}}_n) = n^{-1}\left[\text{tr}\mathbf{V^{-1}KP^{-1}} + \text{tr}\mathbf{V^{-1}P^{-1}}\right]$, where
$\text{tr}\left[\mathbf{V^{-1}KP^{-1}}\right] = \sigma^2\left\{m_T(z^2)[\pi v_T(z)]^{-1} + m_C(z^2)[(1-\pi)v_C(z)]^{-1}\right\}$ and
$\text{tr}\left[\mathbf{V^{-1}P^{-1}}\right] = \sigma^2\left\{[\pi v_T(z)]^{-1} + [(1-\pi)v_C(z)]^{-1}\right\}$.
By letting $\mathbf{D}^t = \begin{pmatrix} 0 & 0 & 1 & 0 \\ 0 & 0 & 0 & 1 \end{pmatrix}$, criteria (3.1) simply become

$$\det \text{var}(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}) = \det\left(n^{-1}\mathbf{D}^t\mathbf{M}_n^{-1}\mathbf{D}\right) = \det\left(\frac{1}{n}\mathbf{V^{-1}P^{-1}}\right) = \left(\frac{\sigma^2}{n}\right)^2 \frac{1}{\pi(1-\pi)v_T(z)v_C(z)},$$

$$\text{tr var}(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}) = \text{tr}\left(\frac{1}{n}\mathbf{V}^{-1}\mathbf{P}^{-1}\right) = \frac{\sigma^2}{n}\left(\frac{1}{\pi v_T(z)} + \frac{1}{(1-\pi)v_C(z)}\right).$$

With regard to the estimation of z^* (assuming $\tau \neq 0$), the MLE of z^* is $\hat{z}_n^* = -\hat{\gamma}_n/\hat{\tau}_n$.
Let $\mathbf{A}^t = \begin{pmatrix} 1 & -1 & 0 & 0 \\ 0 & 0 & 1 & -1 \end{pmatrix}$, then

$$\text{var}(\hat{\gamma}_n; \hat{\tau}_n) = n^{-1}\mathbf{A}^t\mathbf{M}_n^{-1}\mathbf{A} = \frac{\sigma^2}{n}\begin{pmatrix} \frac{m_T(z^2)}{\pi v_T(z)} + \frac{m_C(z^2)}{(1-\pi)v_C(z)} & -\frac{m_T(z)}{\pi v_T(z)} - \frac{m_C(z)}{(1-\pi)v_C(z)} \\ -\frac{m_T(z)}{\pi v_T(z)} - \frac{m_C(z)}{(1-\pi)v_C(z)} & \frac{1}{\pi v_T(z)} + \frac{1}{(1-\pi)v_C(z)} \end{pmatrix}$$

and, via the classical first-order Taylor expansion,

$$\text{var}(\hat{z}_n^*) \approx \tau^{-2}\left[\text{var}(\hat{\gamma}_n) - \frac{2\gamma Cov(\hat{\gamma}_n, \hat{\tau}_n)}{\tau} + \frac{\gamma^2 \text{var}(\hat{\tau}_n)}{\tau^2}\right]$$

so (3.2) follows from simple algebra. By assuming $\boldsymbol{\delta}_n^*$ in (3.3), the ensuing information matrix is

$$\mathbf{M}_n^* = \frac{1}{2\sigma^2}\left(\begin{array}{c|c} \mathbb{I}_2 & m(z)\mathbb{I}_2 \\ \hline m(z)\mathbb{I}_2 & m(z^2)\mathbb{I}_2 \end{array}\right), \tag{A.1}$$

and $\mathbf{M}_n^*$ is invariant with respect to the label switching of T and C. At the same time, for any given design $\boldsymbol{\delta}_n$ generating an information matrix $\mathbf{M}_n$ in (2.3), by the simultaneous permutation of the first two rows and two columns as well as the bottom two rows and the two right-hand columns of $\mathbf{M}_n$, we get the information matrix $\breve{\mathbf{M}}_n$ corresponding to the design $\breve{\boldsymbol{\delta}}_n = \mathbf{1}_n - \boldsymbol{\delta}_n$ which switches T and C. Clearly $\Phi(\breve{\mathbf{M}}_n) = \Phi(\mathbf{M}_n)$ and $\mathbf{M}_n + \breve{\mathbf{M}}_n = 2\mathbf{M}_n^*$, so that by convexity

$$\Phi(\mathbf{M}_n^*) = \Phi\left(2^{-1}\left[\mathbf{M}_n + \breve{\mathbf{M}}_n\right]\right) \leq 2^{-1}\left[\Phi(\mathbf{M}_n) + \Phi(\breve{\mathbf{M}}_n)\right] = \Phi(\mathbf{M}_n).$$

With regard to the estimation of z^*, let $\mathbf{b}^t = (1, -\gamma/\tau)$ and $\tilde{\mathbf{b}}^t = \mathbf{b}^t\mathbf{A}^t$, then criterion (3.2) can be restated as $\mathbf{b}^t\mathbf{A}^t\mathbf{M}_n^{-1}\mathbf{A}\mathbf{b} = \tilde{\mathbf{b}}^t\mathbf{M}_n^{-1}\tilde{\mathbf{b}}$, which is a convex function invariant with respect to label switching of T and C (indeed, the roles of T and C are exchangeable in var $(\hat{\gamma}_n/\hat{\tau}_n)$, that is still the same under the treatment switching). Thus, the optimal design is still the one in (3.3).

A.2 Proof of Proposition 3.1

Due to the convexity of Φ and the linearity of $\mathbf{M}_n$ in terms of π, $m_T(z)$ and $m_T\left(z^2\right)$ (or $v_T(z)$), we could proceed with standard derivation techniques to find the minimum; by noticing that boundary solutions of the form $\pi = 0, 1$ or $v_i(z) = 0$ (for $i = T, C$) are not allowed, since they induce the singularity of $\mathbf{M}_n$ and the divergence of each criterion, it is sufficient to show that the Jacobian of criteria (3.1) vanishes under (3.5). Starting with D_s-optimality, minimizing $\det \text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right)$ is equivalent to maximizing $\pi(1-\pi)v_T(z)v_C(z)$ and from (3.4) it corresponds to maximize

$$g = g(\pi, m_T(z), v_T(z)) = \pi v_T(z)\left[v(z) - \pi v_T(z) - \frac{\pi[m(z) - m_T(z)]^2}{(1-\pi)}\right].$$

Since

$$\frac{\partial g}{\partial m_T(z)} = 2\pi^2 v_T(z)\frac{(m(z) - m_T(z))}{1-\pi},$$

then $\partial g/\partial m_T(z) = 0 \iff m_T(z) = m(z)$. Moreover,

$$\frac{\partial g}{\partial v_T(z)} = \pi\left\{v(z) - \pi v_T(z) - \frac{\pi[m(z) - m_T(z)]^2}{(1-\pi)}\right\} - \pi^2 v_T(z)$$

and, when $m_T(z) = m(z)$, then $\partial g/\partial v_T(z) = 0 \iff v_T(z) = \frac{v(z)}{2\pi}$. Finally,

$$\frac{\partial g}{\partial \pi} = v_T(z)\left[v(z) - \pi v_T(z) - \frac{\pi[m(z) - m_T(z)]^2}{(1-\pi)}\right] - \pi v_T(z)\left[v_T(z) + \frac{[m(z) - m_T(z)]^2}{(1-\pi)^2}\right],$$

that vanishes when $m_T(z) = m(z)$ and $v_T(z) = v(z)/2\pi$.

Analogously, to derive the A_s-optimal design we should minimize

$$h = h(\pi, m_T(z), v_T(z)) = \frac{1}{\pi v_T(z)} + \frac{1}{v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{(1-\pi)}}.$$

Now,

$$\frac{\partial h}{\partial m_T(z)} = -\frac{2\pi[m(z) - m_T(z)]}{(1-\pi)\left[v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{(1-\pi)}\right]^2}$$

and $\partial h/\partial m_T(z) = 0 \iff m_T(z) = m(z)$. In addition,

$$\frac{\partial h}{\partial v_T(z)} = -\frac{1}{\pi v_T(z)^2} + \frac{\pi}{\left[v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{(1-\pi)}\right]^2}$$

and when $m(z) = m_T(z)$ then

$$\frac{\partial h}{\partial v_T(z)} = \frac{-\left[v(z) - \pi v_T(z)\right]^2 + \pi^2 v_T(z)^2}{\pi v_T(z)^2\left[v(z) - \pi v_T(z)\right]^2} = 0 \iff v_T(z) = v(z)/2\pi.$$

Finally, since

$$\frac{\partial h}{\partial \pi} = -\frac{1}{\pi^2 v_T(z)} + \frac{v_T(z) + \frac{[m(z)-m_T(z)]^2}{(1-\pi)^2}}{\left[v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{(1-\pi)}\right]^2}$$

then $\partial h/\partial \pi = 0$ when $m_T(z) = m(z)$ and $v_T(z) = v(z)/2\pi$.

A.3 Proof of Proposition 3.2

When the common variance σ^2 is a priori known, under the alternative hypothesis W_n^2 is distributed according to a non-central χ_1^2 with non-centrality parameter

$$\frac{n\tau^2}{c^t\mathbf{M}_n^{-1}c} = \frac{n\tau^2}{\sigma^2\left(\frac{1}{\pi v_T(z)} + \frac{1}{(1-\pi)v_C(z)}\right)}.$$

Thus, for every sample size n, if the design satisfies (3.5) then from Proposition (3.1) the non-centrality parameter is maximized, leading to the maximization of the power of W_n.

When σ^2 is unknown, the Wald statistic

$$W_n^2 = \frac{n\hat{\tau}_n^2}{\hat{\sigma}_n^2\left(\frac{1}{\pi v_T(z)} + \frac{1}{(1-\pi)v_C(z)}\right)}$$

converges under H_0 to a (central) chi-square with 1 degree of freedom. Assuming that $\lim_{n\to\infty} n^{-1}\mathbf{X}_n^t\mathbf{X}_n = \sigma^2\mathbf{M}^*$ in probability, with $\lim_{n\to\infty}\pi = \pi^* \in (0;1)$ and $\lim_{n\to\infty} v_j(z) = \text{var}_j(Z) > 0$ $(j = T, C)$, under a sequence of contiguous alternatives of the form $H_1 : \tau = \tau^*/\sqrt{n}$ (with $\tau^* \neq 0$), W_n^2 converges in distribution to a non-central χ_1^2 with non-centrality parameter

$$\frac{\tau^{*2}}{c^t\mathbf{M}^{*-1}c} = \frac{\tau^{*2}}{\sigma^2\left(\frac{1}{\pi^*\text{var}_T(Z)} + \frac{1}{(1-\pi^*)\text{var}_C(Z)}\right)},$$

Thus, from the previous arguments, the corresponding optimal design is the one that satisfies (3.5) asymptotically.

A.4 Proof of Theorem 4.1

Since $\tilde{\mathbf{M}}_n = \sigma^2\text{diag}(\mathbf{S},\mathbf{S})\mathbf{M}_n$, then the D-optimality criterion for model (4.1) is

$$\det\text{var}(\hat{\boldsymbol{\zeta}}_n) = \det(n^{-1}\tilde{\mathbf{M}}_n{}^{-1}) = \left(n\sigma^2\right)^{-4}\det\mathbf{L}^{-1}\det\mathbf{Q}^{-1}\det\mathbf{S}^{-2} = \frac{\left(\sigma_T^2\sigma_C^2\right)^2}{n^4\pi^2(1-\pi)^2 v_T(z)v_C(z)},$$

so that, from Theorem 3.1, an allocation $\boldsymbol{\delta}_n^*$ satisfying (3.3) is still D-optimal.

With regard to A-optimality, $\text{tr}\,\text{var}(\hat{\boldsymbol{\zeta}}_n) = n^{-1}\text{tr}(\tilde{\mathbf{M}}_n^{-1})$, where $\text{tr}(\tilde{\mathbf{M}}_n^{-1}) = \text{tr}(\mathbf{V}^{-1}\mathbf{K}\mathbf{P}^{-1}\mathbf{S}^{-1}) + \text{tr}(\mathbf{V}^{-1}\mathbf{P}^{-1}\mathbf{S}^{-1})$; recalling that $\mathbf{K} = \mathbf{V} + \mathbf{H}^2$, then

$$\begin{aligned}\text{tr}(\tilde{\mathbf{M}}_n^{-1}) &= \text{tr}(\mathbf{P}^{-1}\mathbf{S}^{-1}) + \text{tr}(\mathbf{V}^{-1}\mathbf{H}^2\mathbf{P}^{-1}\mathbf{S}^{-1}) + \text{tr}(\mathbf{V}^{-1}\mathbf{P}^{-1}\mathbf{S}^{-1}) \\ &= \frac{\sigma_T^2}{\pi} + \frac{\sigma_C^2}{1-\pi} + \frac{\sigma_T^2}{\pi}\left(\frac{m_T^2(z)+1}{v_T(z)}\right) + \frac{\sigma_C^2}{(1-\pi)}\left(\frac{m_C^2(z)+1}{v_C(z)}\right),\end{aligned}$$

so that, from (3.4),

$$\text{tr}(\tilde{\mathbf{M}}_n^{-1}) = \frac{\sigma_T^2}{\pi} + \frac{\sigma_C^2}{1-\pi} + \frac{\sigma_T^2}{\pi}\left(\frac{m_T^2(z)+1}{v_T(z)}\right) + \sigma_C^2\left(\frac{\left[\frac{m(z)-\pi m_T(z)}{1-\pi}\right]^2 + 1}{v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{(1-\pi)}}\right). \quad \text{(A.2)}$$

Due to the convexity of Φ and the linearity of $\tilde{\mathbf{M}}$ in terms of π, $m_T(z)$ and $m_T\left(z^2\right)$, it is sufficient to show that the Jacobian of (A.2) vanishes under (4.5). Let $\Lambda = m(z) - m_T(z)$, then

$$\frac{\partial \text{tr}(\tilde{\mathbf{M}}_n^{-1})}{\partial \pi} = -\frac{\sigma_T^2}{\pi^2} + \frac{\sigma_C^2}{(1-\pi)^2} - \frac{\sigma_T^2}{\pi^2}\left(\frac{m_T^2(z)+1}{v_T(z)}\right) + \frac{\sigma_C^2}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]} \times$$
$$\left\{\frac{2\Lambda(m(z)-\pi m_T(z))}{(1-\pi)^3} + \frac{\left(v_T(z) + \frac{\Lambda^2}{(1-\pi)^2}\right)\left(\frac{[m(z)-\pi m_T(z)]^2}{(1-\pi)^2}+1\right)}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]}\right\},$$

moreover,

$$\frac{\partial \text{tr}(\tilde{\mathbf{M}}_n^{-1})}{\partial m_T(z)} = \frac{2\sigma_T^2 m_T(z)}{\pi v_T(z)} + \frac{2\sigma_C^2\pi}{(1-\pi)\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]^2}\Bigg\{ - [m(z) - \pi m_T(z)] \times$$
$$\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right] + \left(\left[\frac{m(z)-\pi m_T(z)}{1-\pi}\right]^2 + 1\right)\Lambda\Bigg\},$$

and

$$\frac{\partial \text{tr}(\tilde{\mathbf{M}}_n^{-1})}{\partial v_T(z)} = -\frac{\sigma_T^2}{\pi}\frac{m_T^2(z)+1}{v_T(z)^2} + \sigma_C^2\pi\left\{\frac{\left[\frac{m(z)-\pi m_T(z)}{1-\pi}\right]^2+1}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]^2}\right\}.$$

It's easy to show that when $\pi = \pi_N, m_T(z) = m(z)$ and $v_T(z) = v(z)$, then

$$\frac{\partial \text{tr}(\tilde{\mathbf{M}}_n^{-1})}{\partial \pi} = \frac{\partial \text{tr}(\tilde{\mathbf{M}}_n^{-1})}{\partial m_T(z)} = \frac{\partial \text{tr}(\tilde{\mathbf{M}}_n^{-1})}{\partial v_T(z)} = 0.$$

As far as threshold estimation is concerned,

$$\text{var}(\hat{\gamma}_n; \hat{\tau}_n) = n^{-1}\mathbf{A}^t\tilde{\mathbf{M}}_n^{-1}\mathbf{A} = \begin{pmatrix} \frac{\sigma_T^2 m_T(z^2)}{\pi v_T(z)} + \frac{\sigma_C^2 m_C(z^2)}{(1-\pi)v_C(z)} & -\frac{\sigma_T^2 m_T(z)}{\pi v_T(z)} - \frac{\sigma_C^2 m_C(z)}{(1-\pi)v_C(z)} \\ -\frac{\sigma_T^2 m_T(z)}{\pi v_T(z)} - \frac{\sigma_C^2 m_C(z)}{(1-\pi)v_C(z)} & \frac{\sigma_T^2}{\pi v_T(z)} + \frac{\sigma_C^2}{(1-\pi)v_C(z)} \end{pmatrix},$$

and $\text{var}(\hat{z}_n^*)$ in (4.4) follows via simple algebra. Analogously to the homoscedastic case, the right-hand side of (4.4) could be expressed as $\tilde{\mathbf{b}}^t\tilde{\mathbf{M}}_n^{-1}\tilde{\mathbf{b}}$, namely this is a convex function and therefore it is sufficient to show that its Jacobian vanishes under condition (4.5). From (3.4),

$$\tau^2\tilde{\mathbf{b}}^t\tilde{\mathbf{M}}_n^{-1}\tilde{\mathbf{b}} = \frac{\sigma_T^2}{\pi} + \frac{\sigma_C^2}{1-\pi} + \frac{\sigma_T^2\left[m_T(z) + \frac{\gamma}{\tau}\right]^2}{\pi v_T(z)} + \frac{\sigma_C^2\left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right]^2}{v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{1-\pi}}$$

and, for ease of the presentation, let us also denote the 4th term of the summation by

$$\Psi = \Psi(\pi, m_T(z), v_T(z)) = \frac{\sigma_C^2\left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right]^2}{v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{1-\pi}}.$$

Since $\dfrac{\partial \tau^2 \tilde{\mathbf{b}}^t \tilde{\mathbf{M}}_n^{-1} \tilde{\mathbf{b}}}{\partial \pi} = -\dfrac{\sigma_T^2}{\pi^2} + \dfrac{\sigma_C^2}{(1-\pi)^2} - \dfrac{\sigma_T^2 \left[m_T(z) + \frac{\gamma}{\tau}\right]^2}{\pi^2 v_T(z)} + \dfrac{\partial \Psi}{d\pi}$, where

$$\frac{\partial \Psi}{d\pi} = \sigma_C^2 \frac{2\left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right] \frac{\Lambda}{(1-\pi)^2} \left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{1-\pi}\right] + \left(v_T(z) + \frac{\Lambda^2}{(1-\pi)^2}\right) \left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right]^2}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{1-\pi}\right]^2},$$

and $\dfrac{\partial \tau^2 \tilde{\mathbf{b}}^t \tilde{\mathbf{M}}_n^{-1} \tilde{\mathbf{b}}}{\partial m_T(z)} = \dfrac{2\sigma_T^2 \left[m_T(z) + \frac{\gamma}{\tau}\right]}{\pi v_T(z)} + \dfrac{\partial \Psi}{\partial m_T(z)}$, where

$$\frac{\partial \Psi}{\partial m_T(z)} = \sigma_C^2 \frac{\frac{-2\pi}{1-\pi}\left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right]\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{1-\pi}\right] - \frac{2\Lambda\pi}{1-\pi}\left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right]^2}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{1-\pi}\right]^2},$$

and finally

$$\frac{\partial \tau^2 \tilde{\mathbf{b}}^t \tilde{\mathbf{M}}_n^{-1} \tilde{\mathbf{b}}}{\partial v_T(z)} = -\frac{\sigma_T^2 \left[m_T(z) + \frac{\gamma}{\tau}\right]^2}{\pi v_T(z)^2} + \frac{\pi\sigma_C^2 \left[\frac{m(z)-\pi m_T(z)}{(1-\pi)} + \frac{\gamma}{\tau}\right]^2}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{1-\pi}\right]^2}.$$

When $\pi = \pi_N, m_T(z) = m(z), v_T(z) = v(z)$, then $\frac{\partial \tau^2 \tilde{\mathbf{b}}^t \tilde{\mathbf{M}}_n^{-1} \tilde{\mathbf{b}}}{\partial \pi} = \frac{\partial \tau^2 \tilde{\mathbf{b}}^t \tilde{\mathbf{M}}_n^{-1} \tilde{\mathbf{b}}}{\partial m_T(z)} = \frac{\partial \tau^2 \tilde{\mathbf{b}}^t \tilde{\mathbf{M}}_n^{-1} \tilde{\mathbf{b}}}{\partial v_T(z)} = 0$. With regard to D_s-optimality,

$$\begin{aligned}
\det \text{var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) &= \det\left(n^{-1}\mathbf{D}^t \tilde{\mathbf{M}}_n^{-1} \mathbf{D}\right) = \left[n\sigma^2\right]^{-2} \det\left(\mathbf{D}^t \mathbf{M}_n^{-1} \text{diag}(\mathbf{S}^{-1}, \mathbf{S}^{-1}) \mathbf{D}\right) \\
&= \left[n\sigma^2\right]^{-2} \det\left(\sigma^2 \mathbf{V}^{-1} \mathbf{P}^{-1} \mathbf{S}^{-1}\right) = \frac{\sigma_T^2 \sigma_C^2}{n^2 \pi(1-\pi) v_T(z) v_C(z)},
\end{aligned}$$

which, from Proposition 3.1, is minimized by $\boldsymbol{\delta}_n^*$ satisfying condition (3.5). Finally,

$$\begin{aligned}
\text{tr var}\left(\hat{\beta}_{Tn}, \hat{\beta}_{Cn}\right) &= \text{tr}\left(n^{-1}\mathbf{D}^t \tilde{\mathbf{M}}_n^{-1} \mathbf{D}\right) = \frac{\text{tr}\left(\mathbf{D}^t \mathbf{M}_n^{-1} \text{diag}(\mathbf{S}^{-1}, \mathbf{S}^{-1}) \mathbf{D}\right)}{n\sigma^2} \\
&= \frac{\text{tr}\left(\sigma^2 \mathbf{V}^{-1} \mathbf{P}^{-1} \mathbf{S}^{-1}\right)}{n\sigma^2} = \frac{1}{n}\left\{\frac{\sigma_T^2}{\pi v_T(z)} + \frac{\sigma_C^2}{(1-\pi) v_C(z)}\right\},
\end{aligned}$$

which also coincides with var $(\hat{\tau}_n)$. Thus, to derive the A_s-optimal design

$$\tilde{h} = \tilde{h}(\pi, m_T(z), v_T(z)) = \frac{\sigma_T^2}{\pi v_T(z)} + \frac{\sigma_C^2}{v(z) - \pi v_T(z) - \frac{\pi[m(z)-m_T(z)]^2}{(1-\pi)}}$$

has to be minimized. Since $\frac{\partial \tilde{h}}{\partial m_T(z)} = -2\pi\Lambda\sigma_C^2/(1-\pi)\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]^2$ then $\partial\tilde{h}/\partial m_T(z) = 0 \iff m_T(z) = m(z)$. In addition, $\frac{\partial \tilde{h}}{\partial v_T(z)} = -\frac{\sigma_T^2}{\pi v_T(z)^2} + \frac{\sigma_C^2 \pi}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]^2}$

and, by solving $\partial\tilde{h}/\partial v_T(z) = 0$ we obtain $\pi v_T(z) = \pi_N v(z)$ or $\pi v_T(z) = v(z)[\sigma_T/\{\sigma_T - \sigma_C\}]$; clearly, this latter solution is admissible only when $\sigma_T > \sigma_C$, but under this setting $(1-\pi)v_C(z) = -v(z)[\sigma_C/\{\sigma_T - \sigma_C\}] < 0$ which is impossible. Thus, the only admissible solution is $\pi v_T(z) = \pi_N v(z)$. Finally,

$$\frac{\partial\tilde{h}}{\partial\pi} = -\frac{\sigma_T^2}{\pi^2 v_T(z)} + \sigma_C^2 \frac{v_T(z) + \frac{\Lambda^2}{(1-\pi)^2}}{\left[v(z) - \pi v_T(z) - \frac{\pi\Lambda^2}{(1-\pi)}\right]^2}$$

vanishes when $m_T(z) = m(z)$ and $\pi v_T(z) = \pi_N v(z)$.
Taking now into the problem of testing $H_0 : \tau = 0$ versus $H_1 : \tau \neq 0$, under model (4.1) $\sqrt{n}(\hat{\tau}_n - \tau) \sim \mathrm{N}(0, c^t\tilde{\mathbf{M}}_n^{-1}c)$, where

$$c^t\tilde{\mathbf{M}}_n^{-1}c = \frac{\sigma_T^2}{\pi v_T(z)} + \frac{\sigma_C^2}{(1-\pi)v_C(z)}.$$

Thus, the proof follows directly from Proposition 3.2 by noticing that, when the treatment variances are a priori known, the Wald statistic becomes $W_n = \sqrt{n}\hat{\tau}_n \left\{\frac{\sigma_T^2}{\pi v_T(z)} + \frac{\sigma_C^2}{(1-\pi)v_C(z)}\right\}^{-1/2}$, while when σ_T^2 and σ_C^2 are unknown they should be replaced by consistent estimates.

A.5 Proof of Theorem 5.1

Following Theorem 4.5 of Meyn and Tweedie[36], a Markov chain $\{\mathbf{X}_n\}_{n\in\mathbb{N}}$ on a general state-space $\mathbb{X}$ is bounded in probability if i) $\mathbf{X}_n$ is a T-chain and ii) $\mathbf{X}_n$ satisfies a positive drift condition, namely there exists a norm-like function $V : \mathbb{X} \longrightarrow \mathbb{R}^+$ such that, for some $\eta > 0$ and a compact set $\mathcal{C} \in \mathcal{B}(\mathbb{X})$ (where $\mathcal{B}(\mathbb{X})$ is the Borel sigma algebra), we have

$$\Delta V(\mathbf{X}_n) := \mathbb{E}[V(\mathbf{X}_{n+1}) \mid \mathbf{X}_n] - V(\mathbf{X}_n) \leq -\eta, \qquad \mathbf{X}_n \in \mathcal{C}^c. \tag{A.3}$$

Let now $\mathbf{r}^t = \left(1, z, z^2\right)$ and $I\{E\}$ be the indicator function of the event E. The one step transition kernel for $\{\mathbf{u}_n\}_{n\in\mathbb{N}}$ is

$$\begin{aligned} P(\mathbf{x}, A) &= \Pr(\mathbf{u}_{n+1} \in A \mid \mathbf{u}_n = \mathbf{x}) = \int \Pr(\mathbf{u}_{n+1} \in A \mid \mathbf{u}_n = \mathbf{x}, Z_{n+1} = z) f(z) dz \\ &= \int \Big\{ h\left[2\mathbf{r}^t\mathbf{x} + (1-2\pi^*)\mathbf{r}^t\mathbf{r}\right] I\{\mathbf{x} + (1-\pi^*)\mathbf{r} \in A\} \\ &+ \left(1 - h\left[2\mathbf{r}^t\mathbf{x} + (1-2\pi^*)\mathbf{r}^t\mathbf{r}\right]\right) I\{\mathbf{x} - \pi^*\mathbf{r} \in A\} \Big\} f(z) dz. \end{aligned}$$

To prove that $\{\mathbf{u}_n\}_{n\in\mathbb{N}}$ is a T-chain we need to show that there exists a sampling distribution α and a substochastic transition kernel $T(\mathbf{x}, \cdot)$ such that for any $A \in \mathcal{B}(\mathbb{X})$, $K_\alpha(\mathbf{x}, A) = \sum_{i=1}^{\infty} P^i(\mathbf{x}, A)\alpha(i) \geq T(\mathbf{x}, A)$, where $T(\cdot, A)$ is a lower semicontinuous (LSC) function with $T(\mathbf{x}, \mathbb{X}) > 0$ for all $\mathbf{x} \in \mathbb{X}$. By taking $\alpha(1) = 1$ and 0 otherwise, then $K_\alpha(\mathbf{x}, A) = P(\mathbf{x}, A)$; if we set $T(\mathbf{x}, A) = (\pi^* - \varepsilon) \int I\{\mathbf{x} + (1-\pi^*)\mathbf{r} \in A\} f(z) dz$, then $P(\mathbf{x}, A) \geq T(\mathbf{x}, A)$, recalling that $h(x) \geq \pi^* - \varepsilon > 0$ for any $x \in \mathbb{R}$. Since the indicator function of any open set is LSC, then $T(\mathbf{x}, A)$ is always LSC. Indeed, if A is an

open subset then

$$\begin{aligned}\liminf_{\mathbf{y}\to\mathbf{x}} T(\mathbf{y},A) &= (\pi^*-\varepsilon)\liminf_{\mathbf{y}\to\mathbf{x}}\int I\{\mathbf{y}+(1-\pi^*)\mathbf{r}\in A\}f(z)dz \\ &\geq (\pi^*-\varepsilon)\int \liminf_{\mathbf{y}\to\mathbf{x}} I\{\mathbf{y}+(1-\pi^*)\mathbf{r}\in A\}f(z)dz \\ &\geq (\pi^*-\varepsilon)\int I\{\mathbf{x}+(1-\pi^*)\mathbf{r}\in A\}f(z)dz = T(\mathbf{x},A).\end{aligned} \tag{A.4}$$

Moreover, (A.4) holds even if A is not an open subset; indeed, $T(\mathbf{x},A)$ does not change since the closure of A has zero Lebesgue measure. Finally notice that $T(\mathbf{x},\mathbb{X})>0$ since $\mathbf{x}+(1-\pi^*)\mathbf{r}\in\mathbb{R}^3$ a.s. Thus, $\{\mathbf{u}_n\}_{n\in\mathbb{N}}$ is a T-chain.

In addition, condition (A.3) is satisfied by choosing $V(\mathbf{u}_n)=\|\mathbf{u}_n\|^2$. Indeed, the one-step drift is

$$\begin{aligned}\Delta V(\mathbf{u}_n) &= \mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n] = \mathbb{E}\left[\mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u_n})\mid \mathbf{u}_n, Z_{n+1}=z]\right] \\ &= \int \mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n, Z_{n+1}=z]f(z)dz,\end{aligned}$$

where, letting $\omega_n = 2\mathbf{r}^t\mathbf{u}_n+(1-2\pi^*)\mathbf{r}^t\mathbf{r}$, the inner expectation is equal to

$$\begin{aligned}&\mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n,\mathbf{Z}_{n+1}=z,\delta_{n+1}=1]h(\omega_n)+\\ &\mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n,\mathbf{Z}_{n+1}=z,\delta_{n+1}=0][1-h(\omega_n)].\end{aligned}$$

Since $\mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n,Z_{n+1}=z,\delta_{n+1}=1] = 2(1-\pi^*)\mathbf{r}^t\mathbf{u}_n+(1-\pi^*)^2\mathbf{r}^t\mathbf{r}$ and $\mathbb{E}[V(\mathbf{v}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n,Z_{n+1}=z,\delta_{n+1}=0] = -2\pi^*\mathbf{r}^t\mathbf{u}_n+\pi^{*2}\mathbf{r}^t\mathbf{r}$, then

$$\mathbb{E}[V(\mathbf{u}_{n+1})-V(\mathbf{u}_n)\mid \mathbf{u}_n,Z_{n+1}=z] = \omega_n h(\omega_n)-2\pi^*\mathbf{r}^t\mathbf{u}_n+\pi^{*2}\mathbf{r}^t\mathbf{r},$$

i.e., by simple algebra, $\omega_n\{h(\omega_n)-\pi^*\}+\pi^*(1-\pi^*)\mathbf{r}^t\mathbf{r}$, so that

$$\Delta V(\mathbf{u}_n) = \int \omega_n\{h(\omega_n)-\pi^*\}f(z)dz+\pi^*(1-\pi^*)\int \mathbf{r}^t\mathbf{r}f(z)dz.$$

Note that $\omega_n\{h(\omega_n)-\pi^*\}\leq 0$, since $\omega_n\{h(\omega_n)-\pi^*\}=0$ if and only if $\omega_n=0$ and it is negative otherwise. Indeed, when $\omega_n<0$, it is equal to $\omega_n\varepsilon$, while if $\omega_n>0$ it is equal to $-\omega_n\varepsilon$, so that $-\omega_n\{h(\omega_n)-\pi^*\} = |\omega_n|[h(-|\omega_n|)-\pi^*]$. To verify condition (A.3), we need to show that, for a compact set $\mathcal{C}$, $\Delta V(\mathbf{u}_n)\leq -\eta$, namely

$$\int |\omega_n|[h(-|\omega_n|)-\pi^*]f(z)dz \geq \eta+\pi^*(1-\pi^*)\int \mathbf{r}^t\mathbf{r}f(z)dz, \quad \text{on } \mathcal{C}^c. \tag{A.5}$$

Let $\mathcal{Z}^* = \{z: |2(1,z,z^2)\mathbf{u}_n+(1-2\pi^*)(1,z,z^2)(1,z,z^2)^t|>0\}\subset\mathbb{R}$, then $\Pr(Z_n\in\mathcal{Z}^*)>0$ and the LHS of (A.5) is equal to $\int_{\mathcal{Z}^*}|\omega_n|[h(-|\omega_n|)-\pi^*]f(z)dz$. Let $\mathcal{C}=\{\mathbf{u}_n:\max|2(1,z,z^2)\mathbf{u}_n+(1-2\pi^*)(1,z,z^2)(1,z,z^2)^t|\leq\kappa, z\in\mathcal{Z}^*\}$ be the compact set; in $\mathcal{Z}^*$, the linear transformation $\mathbf{u}_n\to 2\mathbf{r}^t\mathbf{u}_n+(1-2\pi^*)\mathbf{r}^t\mathbf{r}$ is injective and corresponds to an induced norm of $\mathbf{u}_n$, so that for every $\mathbf{u}_n\in\mathcal{C}^c$

$$\int_{\mathcal{Z}^*}|\omega_n|[h(-|\omega_n|)-\pi^*]f(z)dz > \kappa[h(-|\kappa|)-\pi^*]\Pr(Z_n\in\mathcal{Z}^*);$$

so condition (A.3) is verified since $\kappa[h(-|\kappa|)-\pi^*]$ increases in κ, while the right-hand side of (A.5) is bounded. Thus, $\{\mathbf{u}_n\}_{n\in\mathbb{N}}$ is bounded in probability with $\mathbf{u}_n=O_p(1)$ and therefore $n^{-1}\mathbf{u}_n=o_p(1)$.