SOME RECENT DEVELOPMENTS IN THE DESIGN OF ADAPTIVE CLINICAL TRIALS

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ABSTRACT. For clinical trials that compare two or more competing treatments, the literature proposes several randomization rules that aim at favouring, at each stage of the trial, the treatment that appears to be best. In two recent papers the present authors have suggested criteria of optimal allocation that combine inferential precision and ethical gain by means of flexible weights, in order to achieve a good trade-off between efficiency and ethical concerns. The ensuing optimal allocation of the treatments can be targeted by a suitable response-adaptive randomization rule. The purpose of this paper is to illustrate and extend the results previously obtained by the authors to a wider range of statistical models for comparative trials. Methods for implementing these designs are given. Several numerical examples and some simulations are included in order to enhance the applicability.

1. INTRODUCTION

Most clinical trials are carried out to compare different drugs or therapies. Pharmaceutical industries in particular invest very large budgets for research and development of new drugs but recently the increased spending in biomedical research has not reflected in a corresponding increase in benefits. Furthermore, in a clinical trial the ethical concern of assigning treatments to patients so as to care for each of them individually often conflicts with the experimental demands. To overcome this impasse, the FDA Critical Path initiative of 2004 supports and encourages innovative approaches in the design of the trial, in particular the use of adaptive designs. Adaptive designs are sequential procedures that use the available information at each stage to modify aspects of the trial without undermining its validity and integrity. Special cases are

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i) group sequential designs for early termination of the trial due to efficacy or futility through interim analyses;

ii) sample size re-estimation designs;

iii) adaptive dose-finding designs to minimize toxicity while acquiring information on the maximum tolerated dose;

iv) covariate-adjusted designs;

v) adaptive randomization designs for treatment comparison with the ethical aim of skewing allocations towards the best treatment or dropping the less successful treatment arms.

The past decade has witnessed an outburst of books and papers on the topic of adaptive designs in clinical trias, see for instance [5], which pertain mainly to the medical and pharmaceutical literature. At the same time, the topic has aroused a wide interest among statisticians with a more attentive eye to the methodological implications, see for instance the book by Hu and Rosenberger [9].

In two recent papers [2, 3] the present authors have looked at designs of type v) approaching the ethical design problem of individual vs collective ethics via the optimization of specific compromise criteria given by a weighted average of a design optimality measure and a measure of the subjects' risk. The relative weights in the compound criterion have been 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. The purpose of the present paper is to extend the theoretical results obtained in [2, 3] and enhance their applicability by including some numerical examples. For simplicity we consider just two treatments, as is usually the case in Phase III trials, where the aim may be either to estimate the treatment effects separately or, more commonly, to estimate or test their difference.

We shall first of all find the *target* allocation that optimizes a given compound criterion for different response models and different choices of the optimality measures. This target in general depends on the unknown parameters, and we will present adaptive randomization methods that make the experiment converge to the desired target, whatever the true value of the parameters, extending the doubly-adaptive biased coin design of Hu and Zhang [7]. Their properties are discussed

theoretically and illustrated by means of simulations. The last part of the paper discusses a special case of adaptive randomization when one categorical covariate is also observed.

We end this introduction by pointing out that for binary responses, a popular design with an ethical slant is the so-called Play-the-Winner proposed by Zelen [12] and later extended to include randomization [10, 11]. Play-the-Winner is a sequential experiment in which the treatment allocation is repeated for the next patient in case of success, or switched to the other arm in case of failure. It is widely believed to be "an optimal model that minimizes the number of failures" [5], but this claim is not justified by the theory. It can be shown however that when the number of observations goes to infinity the limit allocation of each treatment is inversely proportional to the treatment risk, which clearly always favours the better treatment.

2. THE COMPOUND CRITERION AND THE OPTIMAL ALLOCATION

2.1. **The model.** Given two treatments T_1 and T_2, with n subjects recruited into the trial, let Y_{ik} be the response of patient i ($i = 1, \ldots, n$) to treatment T_k ($k = 1, 2$). Conditionally on the treatment assignment, the responses are usually taken to be independent. Put

$$\mathrm{E}(Y_{ik}) = \mu_k, \quad \mathrm{Var}(Y_{ik}) = \sigma_k^2 \tag{1}$$

and assume a "the-larger-the-μ-the better" scenario. Special cases are

1) homoscedastic responses, i.e. $\sigma_1^2 = \sigma_2^2$;
2) when the responses are binary, with p_1, p_2 being the relative success probabilities:

$$\mathrm{E}(Y_{ik}) = \Pr(Y_{ik} = 1) = p_k, \quad \mathrm{Var}(Y_{ik}) = p_k q_k \tag{2}$$

and $q_k = 1 - p_k$.

We may further assume the dependence of p_k or μ_k on some patient-related covariates.

After n_1 subjects are assigned to T_1 and $n_2 = n - n_1$ to T_2, let π and $1 - \pi$ be the proportions of allocations to T_1 and T_2 respectively. The ML estimators of

μ_1 and μ_2 in general are the sample means and their variance-covariance matrix (exact or asymptotic) is proportional to

$$V = \begin{pmatrix} \dfrac{\sigma_1^2}{\pi} & 0 \\ 0 & \dfrac{\sigma_2^2}{1-\pi} \end{pmatrix}.$$

2.2. **The treatment allocation.** We shall refer to all the desirable treatment allocations as "targets". In Optimal Design Theory, the design problem consists in minimizing a suitably chosen optimality criterion Ψ_I, which measures the loss of potential information ensuing from the experimental design. In particular, the D-optimality criterion $\det(V)$ measures the global variance and the trace criterion $\mathrm{tr}(V)$ measures the variance of the estimated difference $\mu_1 - \mu_2$; under suitable assumptions it also measures the power of Wald's test of the equality of treatment effects. In this setting, popular treatment allocation schemes are the balanced one, $\pi_B^* = 1/2$, which minimizes $\det(V)$, and the well-known Neyman allocation

$$\pi_N^* = \frac{\sigma_1}{\sigma_1 + \sigma_2}, \tag{3}$$

which minimizes $\mathrm{tr}(V)$.

From an ethical viewpoint one possible "optimality criterion" is the proportion Π_W of patients who receive the worse treatment,

$$\Pi_W = \frac{1}{2} + \frac{1}{2}(1 - 2\pi)\,\mathrm{sgn}(\mu_1 - \mu_2)$$

which would be minimized, trivially, by assigning all the patients to the better treatment, if we knew which one this is. This choice however would make the treatment comparison impossible.

In practice, we would most likely wish to simultaneously minimize both the ethical cost and the inferential loss. Note that both are functions of π. A possibility is to measure the trade-off by means of some compromise function, for instance a weighted average of Ψ_I and Π_W, suitably standardized to make them comparable. One way is to set

$$\tilde{\Psi}_I(\pi) = 1 - \left(\frac{\min \Psi_I}{\Psi_I(\pi)}\right)$$

so that both functionals Π_W and $\tilde{\Psi}_I$ range in $[0, 1)$, with 0 being their best value. We can look at the combination

$$\Phi_\omega = \omega \Pi_W + (1 - \omega)\,\tilde{\Psi}_I \tag{4}$$

as the compound criterion to be minimized. We can attempt to find the optimum allocation $\pi^*_\omega = \arg\min_\pi \Phi_\omega$ by differentiation of Φ_ω wrt π, i.e. look for a solution in $(0,1)$ of

$$-\frac{\omega}{(1-\omega)}\frac{\text{sgn}(\mu_1-\mu_2)}{\Psi_I^*} - \frac{\partial}{\partial\pi}\left(\frac{1}{\Psi_I}\right) = 0 \tag{5}$$

where $\Psi_I^* = \min \Psi_I$. The target π^*_ω will in general depend on the following:

- the inferential criterion Ψ_I. As already pointed out, either D-optimality or trace-optimality will in general be chosen as Ψ_I;
- the weights $\omega, 1-\omega$ chosen by the experimenter, with $0 \leq \omega < 1$. They may be fixed or functions of some or all the unknown parameters. The choice of the best weight function $\omega(\cdot)$ in a given applied context is open to discussion, but here are some general remarks:
  (1) the function ω should deal with T_1 and T_2 symmetrically;
  (2) ω should be non-decreasing in the absolute difference of the treatment effects, to make the ethical impact more crucial the more the effects differ, whereas, on the other hand, a small difference is more difficult to detect correctly, so more emphasis is needed on precision (i.e. small ω).
- The unknown parameters. The dependence of the target on the unknown parameters may appear like an unsolvable puzzle, in this as well as in other cases, as for instance the classical Neyman allocation (3). We shall deal with this problem in Section 5.

3. Optimal targets

3.1. **The compound target when Ψ_I is D-optimality.** We assume model (1) and $\Psi_I = \det(V)$. Equation (5) becomes

$$-\frac{\omega}{(1-\omega)}\frac{\text{sgn}(\mu_1-\mu_2)}{4\sigma_1^2\sigma_2^2} = \frac{\partial}{\partial\pi}\left(\frac{\pi(1-\pi)}{\sigma_1^2\sigma_2^2}\right) \tag{6}$$

and

$$\pi^*_\omega = \frac{1}{2} + \text{sgn}(\mu_1-\mu_2)\min\left\{\frac{1}{8}\left(\frac{\omega}{1-\omega}\right),\ \frac{1}{2}\right\}. \tag{7}$$

is the optimum target. The expression for π^*_ω is independent of (σ_1^2, σ_2^2). If $\omega < 4/5$ then

$$\pi^*_\omega = \frac{1}{2} + \text{sgn}(\mu_1 - \mu_2)\frac{1}{8}\left(\frac{\omega}{1-\omega}\right) \in (0,1); \tag{8}$$

otherwise, if $\omega \geq 4/5$, π^*_ω will assign all the subjects to the better treatment.

For binary responses, the optimum target will clearly be

$$\pi^*_\omega = \frac{1}{2} + \text{sgn}(p_1 - p_2)\min\left\{\frac{1}{8}\left(\frac{\omega}{1-\omega}\right),\ \frac{1}{2}\right\}.$$

It is evident that the target allocation (7) will always assign more than half the subjects to the better treatment.

3.1.1. *The choice of the weights.* We can define the "ethical gain" in terms of relative percentage of fewer subjects assigned by π^*_ω to the worse treatment than by the balanced design, namely when $\omega = 0$. Assuming (wlog) $\mu_1 > \mu_2$, it is easy to find the expression of the ethical gain:

$$\frac{(1-\pi^*_B) - (1-\pi^*_\omega)}{1-\pi^*_B} = \frac{\frac{1}{8}\left(\frac{\omega}{1-\omega}\right)}{1/2} = \frac{1}{4}\left(\frac{\omega}{1-\omega}\right). \tag{9}$$

We can measure the inferential loss by

$$\tilde{\Psi}_D = 1 - \frac{\min\det(V)}{\det(V)} = \frac{1}{16}\left(\frac{\omega}{1-\omega}\right)^2. \tag{10}$$

The ethical gain and the inferential loss for the optimal compound target defined in (8) are compared in Table 1.

The percentual ethical gain of the compound target is always greater than the percentual inferential loss, with maximum difference at $\omega = 1/2$.

Another possibility is to let the weight ω depend on the parameters.

Example 1 (Normal case)**.** *For normal responses we could choose*

$$\omega = \frac{4}{5}\left(1 - e^{-\frac{|\mu_1 - \mu_2|}{\sqrt{\sigma_1^2 + \sigma_2^2}}}\right), \tag{11}$$

so that $\pi^*_\omega \in (0,1)$ is satisfied. Letting $\mu_1 > \mu_2$ (wlog), Table 2 shows possible values of $(\mu_1 - \mu_2)/\sqrt{\sigma_1^2 + \sigma_2^2}$ and the corresponding values of the compound target:

ω	π^*_ω	% ethical gain $\left(\frac{\omega}{4(1-\omega)}\right)$	% inferential loss $\left(\left(\frac{\omega}{4(1-\omega)}\right)^2\right)$
0.00	0.50	0.00	0.00
0.10	0.51	2.78	0.08
0.20	0.53	6.25	0.39
0.30	0.55	10.71	1.15
0.40	0.58	16.67	2.78
0.50	0.63	25.00	6.25
0.60	0.69	37.50	14.06
0.70	0.79	58.33	30.03
0.75	0.88	75.00	56.26

TABLE 1. The relative ethical gain and the relative inferential loss for target π^*_ω in (8) as ω varies when $\mu_1 > \mu_2$.

$\frac{\mu_1-\mu_2}{\sqrt{\sigma_1^2+\sigma_2^2}}$	ω	π^*_ω
$\to 0$	$\to 0$	0.500
0.25	0.18	0.527
0.50	0.31	0.557
0.75	0.42	0.591
1.00	0.51	0.628
1.50	0.62	0.705
3.00	0.76	0.896
$\to \infty$	$\to 0.8$	1.000

TABLE 2. Values of the optimum compound target allocation π^*_ω in (8) with ethical weight $\omega = \frac{4}{5}\left(1 - \exp\left(-\frac{|\mu_1-\mu_2|}{\sqrt{\sigma_1^2+\sigma_2^2}}\right)\right)$.

Example 2 (Binary case)**.** *For binary responses a possible choice of the weight function is the one suggested in* [2]*, namely* $\omega(p_1, p_2) = \{(p_1 - p_2)^2 + 1\}/2$*, but the condition* $\omega < 4/5$ *is not always satisfied. Another choice is*

$$\omega(p_1, p_2) = \frac{4}{5}|p_1 - p_2|. \tag{12}$$

Table 3 gives the target allocation to the better treatment as a function of the difference in success probabilities.

$p_1 - p_2$	ω	π^*_ω
$\to 0$	$\to 0$	0.500
0.1	0.08	0.511
0.2	0.16	0.524
0.3	0.24	0.539
0.4	0.32	0.559
0.5	0.40	0.583
0.6	0.48	0.615
0.7	0.56	0.659
0.8	0.64	0.722
0.9	0.72	0.821
1.0	0.80	1.00

TABLE 3. Values of the target π^*_ω as a function of the difference in success probabilities when $\omega = \frac{4}{5}|p_1 - p_2|$.

3.2. **The compound target when Ψ_I is trace-optimality.** Since $\mathrm{tr}(V) = \sigma_1^2/\pi + \sigma_2^2/(1-\pi)$ and $\min \mathrm{tr}(V) = (\sigma_1 + \sigma_2)^2$, equation (5) becomes

$$-\frac{\omega}{1-\omega}\,\frac{\mathrm{sgn}(\mu_1 - \mu_2)}{(\sigma_1+\sigma_2)^2} - \frac{\partial}{\partial \pi}\left(\frac{\pi(1-\pi)}{(\sigma_2^2-\sigma_1^2)\pi + 1}\right) = 0. \tag{13}$$

When $\sigma_1^2 = \sigma_2^2$, equation (6) is identical to (13), so that all the results of Subsection 3.1 apply. Let now $\sigma_1^2 \neq \sigma_2^2$; (13) can be rewritten as a quadratic equation in π:

$$\begin{aligned} -\frac{\omega}{1-\omega}\,\mathrm{sgn}(\mu_1 - \mu_2)\left[(\sigma_2^2-\sigma_1^2)\pi + 1\right]^2 + \\ (\sigma_1+\sigma_2)^2\left[(\sigma_2^2-\sigma_1^2)\pi^2 + 2\sigma_1^2\pi - \sigma_1^2\right] = 0. \end{aligned} \tag{14}$$

If the solution

$$\frac{1}{\frac{\sigma_2^2}{\sigma_1^2} - 1}\left[-1 + \frac{\frac{\sigma_2}{\sigma_1}}{\sqrt{-\frac{\omega}{1-\omega}\,\mathrm{sgn}(\mu_1-\mu_2)\frac{\sigma_2-\sigma_1}{\sigma_1+\sigma_2} + 1}}\right] \tag{15}$$

lies in $(0,1)$, it will give the optimum allocation to T_1 as a function of ω, σ_2/σ_1 and $\mathrm{sgn}(\mu_1 - \mu_2)$. The LHS of (14) is monotonic in $[0,1]$, so the existence of a

unique solution in $(0,1)$ is ensured if the LHS is negative at 0 and positive at 1, namely if

$$-\left(1+\frac{\sigma_1}{\sigma_2}\right)^2 < -\frac{\omega}{1-\omega}\text{sgn}(\mu_1-\mu_2) < \left(1+\frac{\sigma_2}{\sigma_1}\right)^2,$$

which holds if and only if

$$\frac{\omega}{1-\omega} < \frac{(\sigma_1+\sigma_2)^2}{\max(\sigma_1^2,\sigma_2^2)}. \tag{16}$$

We may be able to use some previous knowledge on σ_1^2 and σ_2^2 to choose a weight function that satisfies (16). Since $1 < \frac{\sigma_1+\sigma_2}{\max(\sigma_1,\sigma_2)} \leq 2$, again $\omega < 4/5$ will have to hold true. The condition $\omega < 1/2$, which means that the ethical impact should not prevail over the inferential goal, is enough to guarantee (16) for all σ_1^2 and σ_2^2, but at times may be too restrictive.

Table 4 shows the optimal targets π_ω^* given by (15) for different values of the ratio σ_2/σ_1 and different choices of $\omega/(1-\omega)$, compared with the Neyman allocation.

The top and the bottom parts of Table 4 show the *unfavourable* cases, i.e. $\mu_1 > \mu_2$ with $\sigma_1 < \sigma_2$ or $\mu_1 < \mu_2$ with $\sigma_1 > \sigma_2$, in which Neyman's allocation is unethical, namely it assigns more patients to the worse treatment. The optimal compound target counteracts this effect, especially with a large ω. This points to the need for adaptive weights, for instance by choosing (11) as the weight function. However, Table 4 seems to suggest that the weight ω perhaps should depend also on σ_2/σ_1.

Remark 3. *In this case, whether or not the optimal compound target assigns more than half the subjects to the better treatment depends on the weights and the true values of the parameters. However, there is always an ethical gain, in terms of more subjects assigned by the target π_ω^* to the better treatment than by the inferentially optimum Neyman target π_N^*. To show this, it is sufficient to check that sgn$(\mu_1-\mu_2)$ = sgn$(\pi_\omega^*-\pi_N^*)$, replacing π_ω^* by (15).*

Assuming $\mu_1 > \mu_2$ (wlog), the ethical gain is given by

$$\frac{\pi_\omega^*-\pi_N^*}{1-\pi_N^*}$$

		$\frac{\omega}{1-\omega}$							
	$\frac{\sigma_2}{\sigma_1}$	0.20	0.33	0.50	1.00	1.50	2.00	3.00	π_N^*
$\mu_1 > \mu_2$	5.00	0.18	0.19	0.21	0.32	1.00	1.00	1.00	0.17
	4.00	0.22	0.23	0.25	0.35	0.78	1.00	1.00	0.20
	2.00	0.36	0.37	0.40	0.48	0.61	0.82	1.00	0.33
	1.50	0.42	0.44	0.46	0.54	0.63	0.75	1.00	0.40
	1.33	0.45	0.47	0.49	0.57	0.65	0.74	0.98	0.43
	1.00	0.52	0.54	0.56	0.63	0.69	0.75	0.88	0.50
	0.80	0.58	0.60	0.61	0.67	0.72	0.77	0.85	0.56
	0.50	0.69	0.70	0.72	0.76	0.79	0.82	0.86	0.67
	0.33	0.79	0.80	0.81	0.83	0.85	0.87	0.90	0.77
	0.25	0.81	0.82	0.83	0.86	0.87	0.89	0.91	0.80
	0.20	0.85	0.85	0.86	0.88	0.89	0.91	0.92	0.83
$\mu_1 < \mu_2$	5.00	0.15	0.15	0.14	0.12	0.11	0.09	0.08	0.17
	4.00	0.19	0.18	0.17	0.14	0.13	0.11	0.09	0.20
	2.00	0.31	0.30	0.28	0.24	0.21	0.18	0.14	0.33
	1.50	0.38	0.36	0.34	0.30	0.25	0.21	0.15	0.40
	1.33	0.41	0.39	0.37	0.32	0.27	0.23	0.15	0.43
	1.00	0.48	0.46	0.44	0.37	0.31	0.25	0.12	0.50
	0.80	0.53	0.51	0.49	0.42	0.34	0.26	0.06	0.56
	0.50	0.64	0.63	0.60	0.52	0.39	0.18	0.00	0.67
	0.33	0.75	0.74	0.71	0.61	0.35	0.00	0.00	0.77
	0.25	0.78	0.77	0.75	0.65	0.22	0.00	0.00	0.80
	0.20	0.82	0.81	0.79	0.68	0.00	0.00	0.00	0.83

TABLE 4. Optimal target π_ω^* for different values of σ_2/σ_1 and $\omega/(1-\omega)$ when Ψ_I is the trace, compared with Neyman's π_N^*.

and the loss of efficiency is

$$\tilde{\Psi}_{\text{tr}} = 1 - \frac{\min \text{tr}(V)}{\text{tr}(V)} = 1 - (\sigma_1 + \sigma_2)^2 \frac{\pi_\omega^* (1 - \pi_\omega^*)}{(\sigma_2^2 - \sigma_1^2)\pi_\omega^* + \sigma_1^2} \,.$$

The comparisons are shown in Figure 1, for different values of the ratio σ_2/σ_1 equal to 4, 1.5, 0.75 and 0.25 (clockwise).

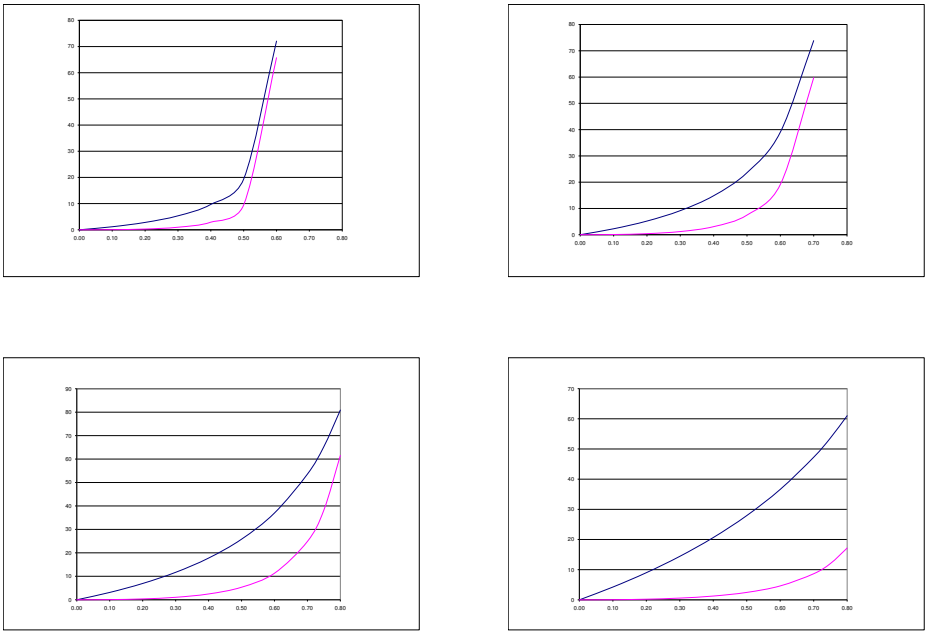

FIGURE 1

For the binary model (2), equation (14) becomes

$$-\frac{\omega}{1-\omega}\,\mathrm{sgn}(p_1-p_2)\left[\left(\frac{p_2q_2}{p_1q_1}-1\right)\pi+1\right]^2+\left(\sqrt{\frac{p_2q_2}{p_1q_1}}+1\right)^2\left[\left(\frac{p_2q_2}{p_1q_1}-1\right)\pi^2+2\pi-1\right]=0 \tag{17}$$

and condition (16) translates to

$$\frac{\omega}{1-\omega}<\frac{\left(\sqrt{p_1q_1}+\sqrt{p_2q_2}\right)^2}{\max(p_1q_1,p_2q_2)}. \tag{18}$$

When $p_1 > p_2$, the unfavourable case occurs if $p_1q_1 \le p_2q_2$. In Table 5 we show the optimum compound targets that correspond to different choices of the weight ratio $\omega/(1-\omega)$ and different values of p_1, p_2, and compare them with the Neyman allocation π^*_N and the Play-the-Winner target $\pi^*_{PW} = \dfrac{q_2}{q_1+q_2}$.

Although π^*_{PW} always assigns more than half the subjects to the better treatment, the PW target assignment would perform very badly for inference.

		$\frac{\omega}{1-\omega}$									
p_1	p_2	0.05	0.11	0.25	1.00	1.50	2.00	2.50	3.00	π_N^*	π_{PW}^*
0.10	0.05	0.586	0.593	0.609	0.688	0.735	0.777	0.816	0.851	0.579	0.514
0.20	0.05	0.653	0.660	0.674	0.741	0.777	0.808	0.834	0.858	0.647	0.543
0.20	0.10	0.578	0.585	0.601	0.682	0.730	0.774	0.814	0.851	0.571	0.529
0.40	0.05	0.698	0.704	0.717	0.775	0.805	0.830	0.851	0.869	0.692	0.613
0.40	0.20	0.557	0.564	0.581	0.666	0.717	0.766	0.811	0.854	0.551	0.571
0.40	0.35	0.513	0.521	0.538	0.630	0.691	0.752	0.812	0.871	0.507	0.520
0.65	0.40	0.500	0.507	0.525	0.620	0.684	0.748	0.814	0.880	0.493	0.632
0.65	0.60	0.500	0.507	0.525	0.620	0.684	0.748	0.814	0.880	0.493	0.533
0.95	0.65	0.319	0.326	0.343	0.465	0.606	0.881	1.000	1.000	0.314	0.875
0.95	0.85	0.385	0.392	0.410	0.524	0.625	0.760	0.954	1.000	0.379	0.750

TABLE 5. Optimal target π_ω^* for different values of p_1, p_2 and $\omega/(1-\omega)$ when Ψ_I is the trace, compared with Neyman's π_N^* and the Play-the-Winner target π_{PW}^*.

4. DIFFERENT CRITERIA FOR THE BINARY MODEL

4.1. **Changing the measure of ethical loss.** For binary responses, another possible measure of ethical loss is the expected proportion of failures:

$$E_F(\pi_1, \pi_2) = \pi_1 q_1 + \pi_2 q_2,$$

which is related to Π_W by a linear transformation:

$$\begin{aligned}\frac{E_F - q_{\min}}{q_{\max} - q_{\min}} &= \frac{\pi_1 q_1 + (1-\pi_1) q_2 - q_{\min}}{|p_1 - p_2|} \\ &= \frac{1}{2} + \left(\frac{1}{2} - \pi_1\right) \operatorname{sgn}(p_1 - p_2) = \Pi_W.\end{aligned}$$

If we minimize the compound criterion

$$\Phi_\omega^{(1)} = \omega E_F + (1-\omega)\, \tilde{\Psi}_I,$$

this is equivalent to minimizing criterion (4) with different weights. More precisely,

$$\arg\min_{\pi\in[0,1]}\left[\omega E_F+(1-\omega)\,\tilde{\Psi}_I\right]=\arg\min_{\pi\in[0,1]}\left[\bar{\omega}\Pi_W+(1-\bar{\omega})\,\tilde{\Psi}_I\right]$$
$$\text{where } \bar{\omega}=\frac{\omega\cdot|p_1-p_2|}{\omega\cdot|p_1-p_2|+1-\omega}$$

Basically, we are re-scaling the weight ratio, namely $\frac{\omega}{1-\omega}|p_1-p_2|=\frac{\varpi}{1-\varpi}$. The results of Sections 3.1 and 3.2 can be applied after suitable changes. In particular,

- for the determinant: the choice $\omega<4/5$ ensures $\bar{\omega}<4/5$ and in this case the optimal target is

$$\pi^*_\omega=\frac{1}{2}+(p_1-p_2)\frac{1}{8}\frac{\omega}{1-\omega}; \tag{19}$$

- for the trace: replace $\frac{\omega}{1-\omega}$ by $\frac{\omega}{1-\omega}\cdot|p_1-p_2|$ in equation (14) and replace condition (18) by

$$\frac{\omega\cdot|p_1-p_2|}{1-\omega}<\frac{\left(\sqrt{p_1q_1}+\sqrt{p_2q_2}\right)^2}{\max(p_1q_1,p_2q_2)}.$$

4.2. **Changing the compound criterion.** Now we want to deal with an altogether different compound criterion, the one that was assumed in [2], namely:

$$\Phi^{(2)}_\omega(\pi_1,\pi_2)=\omega\left(\frac{E_F(\pi_1,\pi_2)}{\min E_F}\right)+(1-\omega)\left(\frac{\Psi_I(\pi_1,\pi_2)}{\min\Psi_I}\right). \tag{20}$$

Since the minimum value of E_F is simply $q_{\min}$, by differentiation the defining equation of this new compound target is

$$-\omega\frac{(p_1-p_2)}{q_{\min}}+(1-\omega)\,\frac{1}{\Psi^*_I}\frac{\partial\Psi_I}{\partial\pi}=0. \tag{21}$$

4.3. **The targets wrt criterion (20).** If $\Psi_I=D$-optimality, equation (21) becomes

$$-\frac{\omega}{1-\omega}\,\frac{p_1-p_2}{q_{\min}}4p_1q_1p_2q_2+\frac{\partial}{\partial\pi}\left(\frac{p_1q_1p_2q_2}{\pi(1-\pi)}\right)=0,$$

i.e.

$$-\frac{\omega}{1-\omega}\,\frac{4(p_1-p_2)}{q_{\min}}+\frac{2\pi-1}{\pi^2(1-\pi)^2}=0, \tag{22}$$

and the optimal target is obtained by solving (22) in $(0,1)$. Since the LHS of (22) is monotonic and as $\pi\to0$ and 1, the limits are $-\infty$ and $+\infty$, respectively, there is a unique solution in $(0,1)$. The important difference from considering criterion

(4) is that in this case the optimal solution depends on the actual values of p_1, p_2 and not just on the sign of their difference.

Remark 4. *It is evident from (22) that this target will always assign more than half the subjects to the better treatment, since sgn*$(2\pi - 1) =$ *sgn*$(p_1 - p_2)$.

If $\Psi_I =$ trace-optimality, the defining equation is

$$\frac{\omega}{(1-\omega)} \frac{p_1 - p_2}{q_{\min}} \left(\sqrt{p_1 q_1} + \sqrt{p_2 q_2}\right)^2 - \frac{\partial}{\partial \pi} \left(\frac{p_1 q_1}{\pi} + \frac{p_2 q_2}{1-\pi} \right) = 0$$

namely

$$\frac{\omega}{(1-\omega)} \frac{p_1 - p_2}{q_{\min}} \left(\sqrt{\frac{p_2 q_2}{p_1 q_1}} + 1 \right)^2 - \frac{\left(\frac{p_2 q_2}{p_1 q_1} - 1\right) \pi^2 + 2\pi - 1}{\pi^2 (1-\pi)^2} = 0\,. \tag{23}$$

Remark 5. *It is shown in* [2] *that with this target allocation, the majority of subjects will receive the better treatment if the weight function is chosen so that* $\omega(x, y) \geq 1/2$ *when* $x + y > 1$.

Table 6 shows the values of the compound targets that solve (22) and (23), corresponding to fixed weight $\omega = 1/2$ ($\pi^*_{\omega=1/2}$ and $\pi^{**}_{\omega=1/2}$, respectively) and to $\omega = (|p_1 - p_2| + 1)/2$ ($\pi^*_{\omega_p}$ and $\pi^{**}_{\omega_p}$, respectively) for several choices of p_1 and p_2.

The targets $\pi^{**}_{\omega=1/2}$ and $\pi^{**}_{\omega_p}$ assign more patients to the better treatment, whereas the bottom part of Table 6 (outlined) shows the values of (p_1, p_2) for which the Neyman target penalizes the better treatment. Clearly the values of $\pi^*_{\omega=1/2}$ and $\pi^*_{\omega_p}$, and of $\pi^{**}_{\omega=1/2}$ and $\pi^{**}_{\omega_p}$ are very close when $|p_1 - p_2|$ is small.

5. Convergence to the optimal allocation: response-adaptive experiments

As shown previously, the target allocation depends in general on some or all the unknown parameters of the model, e.g. $\pi^*_\omega = \pi^*_\omega(\theta)$ with $\theta \subseteq \{\mu_1, \sigma_1^2; \mu_2, \sigma_2^2\}$, and when this function is continuous *response-adaptive* procedures may be called for. These designs, also called *response-driven* or *data-dependent*, use the observed responses as well as past allocations to modify the experiment as we go along in order to gradually approach the desired target allocation.

		D-optimality		trace-optimality			
p_1	p_2	$\pi^*_{\omega=1/2}$	$\pi^*_{\omega_p}$	$\pi^{**}_{\omega=1/2}$	$\pi^{**}_{\omega_p}$	π^*_N	π^*_{PW}
0.10	0.05	0.507	0.508	0.586	0.587	0.579	0.514
0.20	0.05	0.523	0.531	0.668	0.675	0.647	0.543
0.20	0.10	0.516	0.519	0.587	0.590	0.571	0.529
0.40	0.05	0.570	0.631	0.744	0.782	0.692	0.613
0.40	0.20	0.541	0.561	0.590	0.609	0.551	0.571
0.40	0.35	0.510	0.512	0.517	0.518	0.507	0.520
0.65	0.40	0.584	0.630	0.578	0.624	0.493	0.632
0.65	0.60	0.518	0.520	0.511	0.513	0.493	0.533
0.95	0.65	0.802	0.852	0.724	0.796	0.314	0.875
0.95	0.85	0.686	0.709	0.599	0.629	0.379	0.750

TABLE 6. Values of the compound targets for $D-$ and trace-optimality, corresponding to $\omega = 1/2$ and $\omega_p = (|p_1 - p_2|+1)/2$, for different choices of p_1 and p_2.

Now we briefly describe the general framework of these sequential methods. Starting with n_0 observations on each treatment, usually assigned by using restricted randomization, e.g. permuted block designs, an initial non-trivial parameter estimation $\hat{\theta}_0$ is derived. Then, at each step n ($n > 2n_0$) let $\hat{\theta}(n)$ be a consistent parameter estimator of θ based on the first n observations, so that the optimal target will be estimated by all the data up to that step. Let $\hat{\pi}^*_\omega(n) = \pi^*_\omega(\hat{\theta}(n))$. Moreover, let $N_1(n)$ and $N_2(n)$ be the number of patients assigned to T_1 and T_2, respectively, with $N_1(n) + N_2(n) = n$; additionally, $\pi(n) = n^{-1}N_1(n)$ is the random proportion of allocation to T_1 and, symmetrically, $1 - \pi(n)$ to T_2. When patient $n + 1$ is ready to be randomized, s/he will be assigned to T_1 with probability P_{n+1} (consequently, to T_2 with probability $1 - P_{n+1}$) and the problem consists in choosing the allocation probabilities $\{P_n, n \geq 1\}$ so that, as n tends to infinity, $\pi(n)$ converges to $\pi^*_\omega(\theta)$ in some sense.

One of the most effective family of randomization procedures is the Doubly Adaptive Biased Coin Design (D-BCD) analyzed by Hu and Zhang [7] (see also references therein). The rationale behind this procedure consists in favouring the

allocation of a given treatment, the more so the more its current allocation proportion is smaller than the current estimate of the target. The D-BCD consists in assigning treatment T_1 to subject $n+1$ with probability $P_{n+1} = g(\pi(n); \hat{\pi}^*_\omega(n))$ for all $n > 2n_0$, where the allocation function $g(\cdot\,;\cdot)$ is chosen by the experimenter so as to force the treatment assignments on the basis of some measure of the "dissimilarity" between their actual allocation proportion x and the current estimate of the optimal target y. The function g needs to satisfy the following conditions:

i) $g(x; y)$ is continuous on $(0; 1)^2$;

ii) $g(x; x) = x$;

iii) $g(x; y)$ is decreasing in x and increasing in y;

iv) $g(x; y) = 1 - g(1 - x; 1 - y)$ for all $x, y \in (0; 1)^2$.

Observe that the D-BCD will force the allocation proportion to the target, since from conditions ii) and iii), when $x > y$ then $g(x, y) < y$, whereas if $x < y$, then $g(x, y) > y$. However, condition i) is quite restrictive since does not include several widely-known procedures based on discontinuous allocation functions such as Efron's Biased coin design and its extensions [8], while condition iv) simply guarantees that T_1 and T_2 are treated symmetrically.

The following result ensures the convergence of the D-BCD to the chosen compound optimal target allocation $\pi^*_\omega(\theta)$ (see for instance [7]):

Proposition 6. *If the compound optimal target $\pi^*_\omega(\theta) \in (0, 1)$ and is continuous in θ, adopting the D-BCD*

$$\lim_{n\to\infty} \pi(n) = \pi^*_\omega(\theta) \qquad \textit{and} \qquad \lim_{n\to\infty} \hat{\theta}(n) = \theta \quad a.s.$$

Now we give some examples belonging to the D-BCD family:

Method 1. The most "intuitive" allocation rule consists in letting $g(x; y) = y$; this means that treatment T_1 will be assigned to subject $n + 1$ with probability

$$P_{n+1} = \hat{\pi}^*_\omega(n)\,. \tag{24}$$

When estimation is made by ML, this procedure is called the Sequential Maximum Likelihood (SML) or recursive Maximum Likelihood design. See [1] and references therein.

Method 2. Hu and Zhang [7] suggest the following family of allocation functions

$$g_\gamma(x;y) = \frac{y(y/x)^\gamma}{y(y/x)^\gamma + (1-y)[(1-y)/(1-x)]^\gamma}\,, \tag{25}$$

where the non-negative parameter γ controls the degree of randomness of each allocation: if $\gamma \to 0$ the randomization function does not dependent on the current allocation proportion and this procedure corresponds to the SML design in (24), whereas as γ grows the allocation tends to be forced deterministically to the estimated target.

Method 3. A new proposal of allocation function is:

$$g(x;y) = \frac{F\left[G\left(\frac{y}{x}\right)F^{-1}(y)\right]}{F\left[G\left(\frac{y}{x}\right)F^{-1}(y)\right] + F\left[G\left(\frac{1-y}{1-x}\right)F^{-1}(1-y)\right]}, \tag{26}$$

where $F(z), G(z) : \mathbb{R}^+ \to \mathbb{R}^+$ are continuous and increasing functions and $G(1) = 1$. Note that if $F(z) = z$ and $G(z) = z^\gamma$ one obtains $g_\gamma(x;y)$ in (25).

Example 7. *Set $G(z) = z$. We let*

$$\tilde{g}(x;y) = \frac{F\left(\frac{y}{x}F^{-1}(y)\right)}{F\left(\frac{y}{x}F^{-1}(y)\right) + F\left(\frac{1-y}{1-x}F^{-1}(1-y)\right)}, \tag{27}$$

where $F(z) = \frac{2}{\sqrt{\pi}}\int_0^z e^{-t^2}dt$ (this F is called the error function).

Figure 2 shows the behaviour of the function $\tilde{g}$ in (27). Table 7 shows the com-

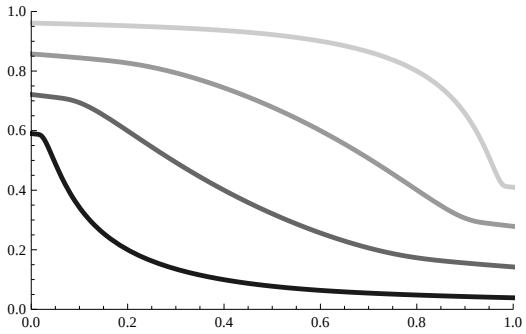

FIGURE 2. Plots of $\tilde{g}(x;y)$ as x varies in $(0;1)$. The values of y from the bottom curve to the top curve are: 0.2, 0.4, 0.6 and 0.8, respectively.

parisons between the above mentioned randomization functions, i.e. Method 1, Method 2 and Method 3, in order to stress the different impact of these procedures

in terms of treatment allocations when both the target estimate and the allocation proportion vary.

x	y	g_0 (SML)	g_1	g_2	$\tilde{g}$
$\to 0$	0.1	0.1	1.000	1.000	0.537
$\to 0$	0.3	0.3	1.000	1.000	0.653
$\to 0$	0.5	0.5	1.000	1.000	0.792
$\to 0$	0.7	0.7	1.000	1.000	0.916
$\to 0$	0.9	0.9	1.000	1.000	0.990
0.2	0.1	0.1	0.047	0.022	0.051
0.2	0.3	0.3	0.424	0.557	0.407
0.2	0.5	0.5	0.800	0.941	0.735
0.2	0.7	0.7	0.956	0.995	0.897
0.2	0.9	0.9	0.997	0.999	0.988
0.4	0.1	0.1	0.018	0.003	0.025
0.4	0.3	0.3	0.216	0.151	0.227
0.4	0.5	0.5	0.600	0.692	0.585
0.4	0.7	0.7	0.891	0.966	0.859
0.4	0.9	0.9	0.992	0.999	0.984
0.6	0.1	0.1	0.008	0.001	0.016
0.6	0.3	0.3	0.109	0.034	0.141
0.6	0.5	0.5	0.400	0.308	0.415
0.6	0.7	0.7	0.784	0.850	0.773
0.6	0.9	0.9	0.982	0.997	0.975
0.8	0.1	0.1	0.003	$\simeq 0$	0.012
0.8	0.3	0.3	0.044	0.005	0.103
0.8	0.5	0.5	0.200	0.059	0.265
0.8	0.7	0.7	0.577	0.443	0.593
0.8	0.9	0.9	0.953	0.979	0.949

TABLE 7. Values of the randomization function g_γ in (25) with $\gamma = 0$, namely the SML design, $\gamma = 1$, $\gamma = 2$ and $\tilde{g}$ in (27).

The SML design (Method 1) is not affected by the current allocation proportions but depends only on the current estimate of the target. As an example, when

$y = 0.7$ the SML design favours the allocation of T_1 by assigning T_1 with probability 0.7, both in case of $x = 0.05$ and $x = 0.8$. Method 2, however, strongly depends on the current allocation proportion. Indeed, the top part of Table 7 shows that if treatment T_1 has (almost) never been assigned, then it will be allocated with probability 1 even if the target allocation is extremely small (e.g. $y = 0.1$ or $y = 0.3$). Furthermore, starting from $\gamma = 2$ Method 2 tends to be highly deterministic. On the contrary, the proposed $\tilde{g}$ in (27) has an interesting behaviour as regards the drawbacks of Methods 1 and 2, since it forces the allocation decisively onto the target, when needed, guaranteeing at the same time a suitable degree of randomness.

5.1. **Simulations.** In order to carry out some finite sample comparisons between the three above-mentioned allocation rules, namely Method 1 (i.e. the SML design), Method 2 (Hu and Zhang's g_γ in (25) with $\gamma = 1$) and Method 3 (rule $\tilde{g}$ in (27)), we have performed a simulation study where we take into account normal and binary responses and also the two different compound criteria (4) and (20). Figures 3-7 below show the behaviour of the allocation proportion of treatment T_1 as it approaches the compound target. Each figure shows the plots of 10 simulations with $n = 1000$ subjects and $n_0 = 4$. As regards the normal model (Fig. 3), we set $\mu_1 = 1$, $\mu_2 = 0$ and three different scenarios for the standard deviations, i.e. $\sigma_1 = 1$ and $\sigma_2 = 5$, $\sigma_1 = 5$ and $\sigma_2 = 1$, $\sigma_1 = 1$ and $\sigma_2 = 1.1$, where the chosen optimum compound target is (8) with weight function ω in (11). Moreover, in the binary case we have considered both compound criteria (4) (Fig. 4-5) and (20) (Fig. 6-7) assuming the trace-optimality criterion. Regarding criterion (4), we have taken into account $\omega = \frac{4}{5}|p_1 - p_2|$ (Fig. 4) and $\omega = \frac{1}{2}$ (Fig. 5), while for criterion (20) we have assumed $\omega = \frac{|p_1-p_2|+1}{2}$ (Fig. 6) and $\omega = \frac{1}{2}$ (Fig. 7). We have taken into account three different parameter settings, namely $p_1 = 0.3, p_2 = 0.2$ (top panel of the figures), $p_1 = 0.65, p_2 = 0.4$ (middle panel of the figures) and $p_1 = 0.95, p_2 = 0.65$ (bottom panel of the figures).

In general, Methods 2 and 3 perform better than Method 1. Indeed, as theoretically shown in [7], the SML design is characterized by slower convergence, since it is based only on the current estimate of the target (independently of the allocation

proportion) and the MLE are characterized by strong variability for small n. Moreover, graphical evidence points to the fact that Methods 2 and 3 guarantee stable behaviour around the target starting from $n = 300$ units, whereas all the procedures have strong variability for small sample trials (in particular when $n < 200$).

As regards normal responses (Fig. 3), simulations show that the convergence is not affected by the values of the standard deviations and Methods 2 and 3 guarantee a better convergence to the target. Whereas, for binary response trials (Fig. 4-7) the variability of the procedures is limited when the responses are approximately homoscedastic (i.e. $p_1 = 0.65$ and $p_2 = 0.4$).

Furthermore, as regards the comparison between the two different compound criteria, there seem to be no significant differences in terms of convergence to the corresponding targets.

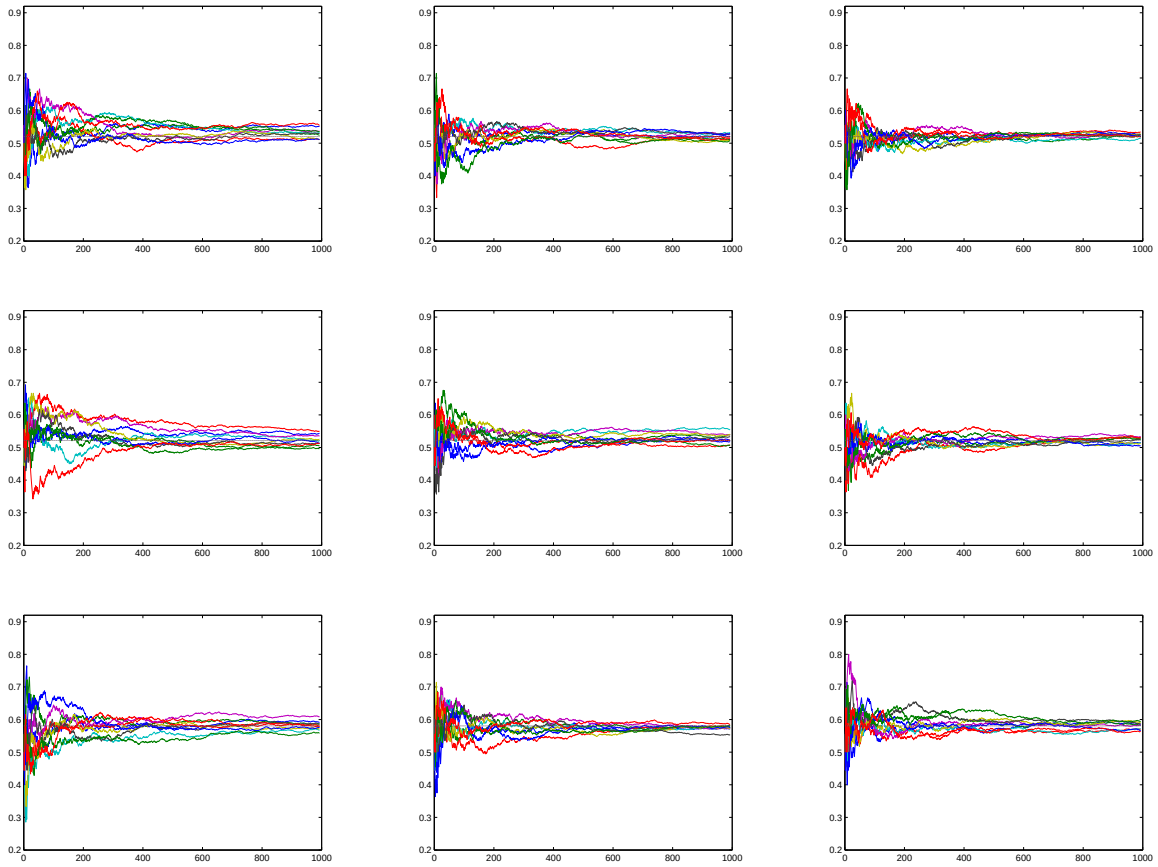

FIGURE 3. Convergence to the optimum compound target π^*_ω in (8) for methods 1 (first column), 2 (second column) and 3 (third column) for normal responses with $\omega = \frac{4}{5}\left[1 - \exp\left(-\frac{|\mu_1-\mu_2|}{\sqrt{\sigma_1^2+\sigma_2^2}}\right)\right]$ and $\mu_1 = 1$, $\mu_2 = 0$ for $\sigma_1 = 1$ and $\sigma_2 = 5$ (top), $\sigma_1 = 5$ and $\sigma_2 = 1$ (middle), $\sigma_1 = 1$ and $\sigma_2 = 1.1$ (bottom).

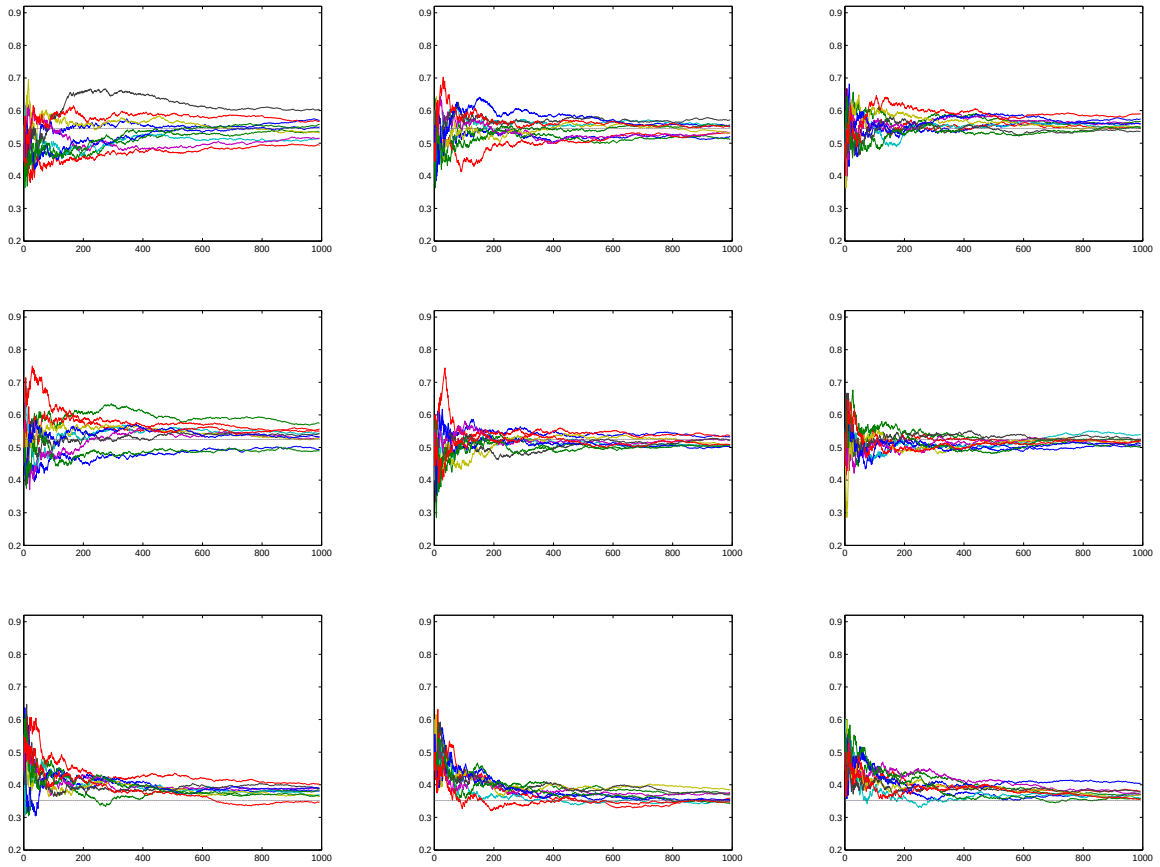

FIGURE 4. Convergence to the optimum compound target π^*_ω solving (17) for methods 1 (first column), 2 (second column) and 3 (third column) for binary responses with $\omega = \frac{4}{5}|p_1 - p_2|$ and $p_1 = 0.3$, $p_2 = 0.2$ (top), $p_1 = 0.65$, $p_2 = 0.4$ (middle) and $p_1 = 0.95$, $p_2 = 0.65$ (bottom).

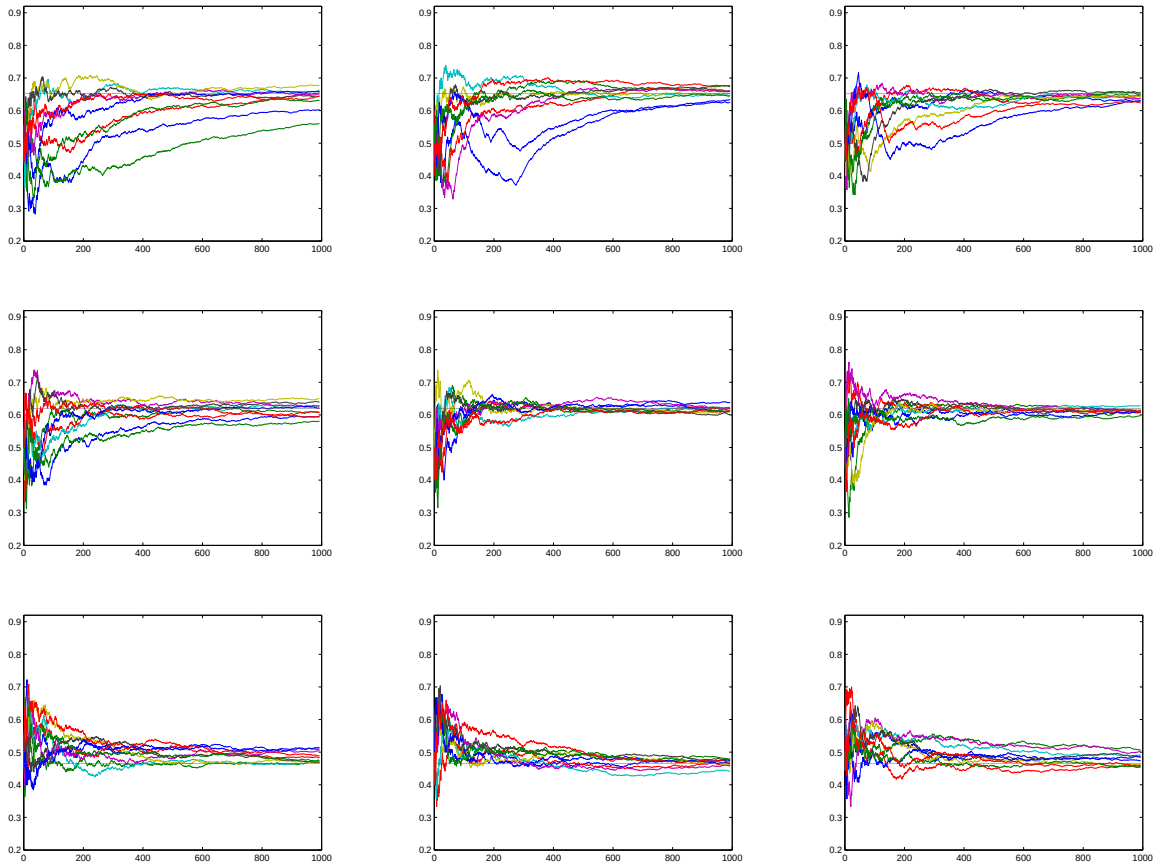

FIGURE 5. Convergence to the optimum compound target π^*_ω solving (17) for methods 1 (first column), 2 (second column) and 3 (third column) for binary responses with $\omega = \frac{1}{2}$ and $p_1 = 0.3$, $p_2 = 0.2$ (top), $p_1 = 0.65$, $p_2 = 0.4$ (middle) and $p_1 = 0.95$, $p_2 = 0.65$ (bottom).

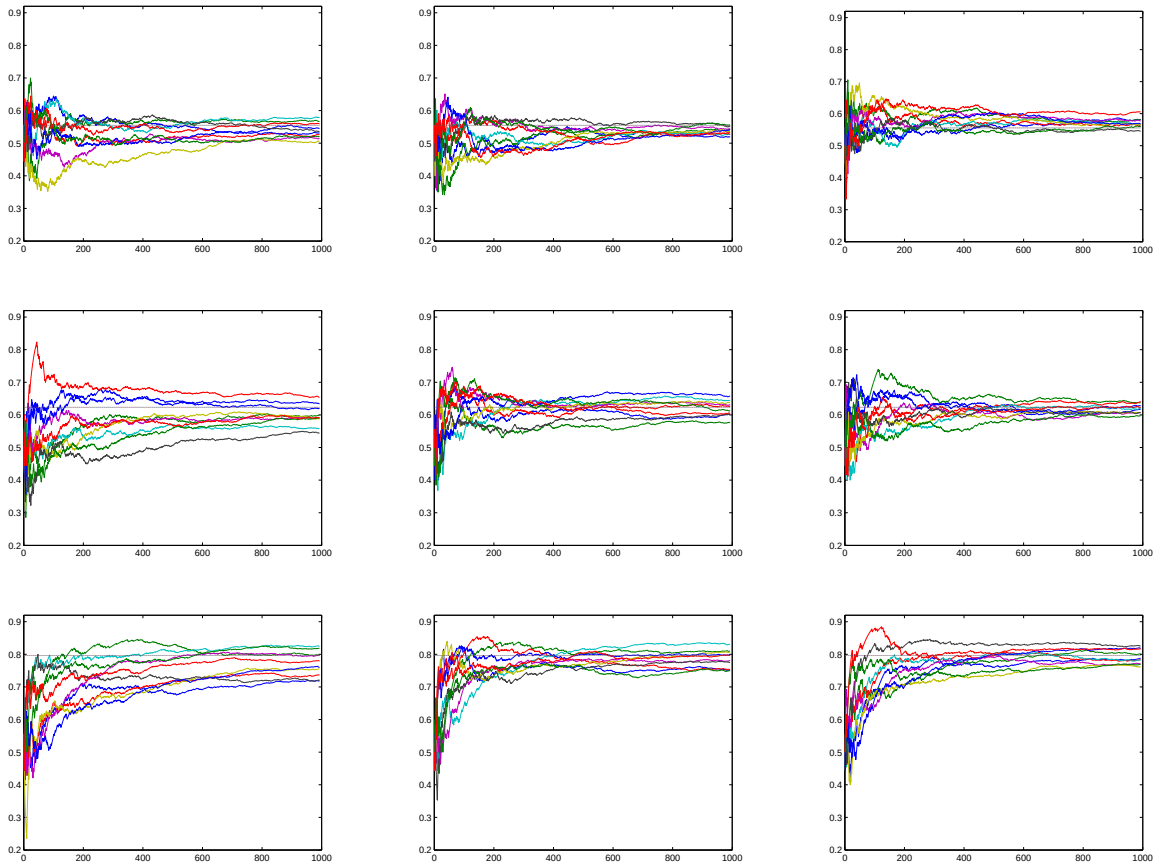

FIGURE 6. Convergence to the optimum compound target π^*_ω solving (23) for methods 1 (first column), 2 (second column) and 3 (third column), for binary responses with $\omega = \frac{|p_1-p_2|+1}{2}$ and $p_1 = 0.3$, $p_2 = 0.2$ (top), $p_1 = 0.65$, $p_2 = 0.4$ (middle) and $p_1 = 0.95$, $p_2 = 0.65$ (bottom).

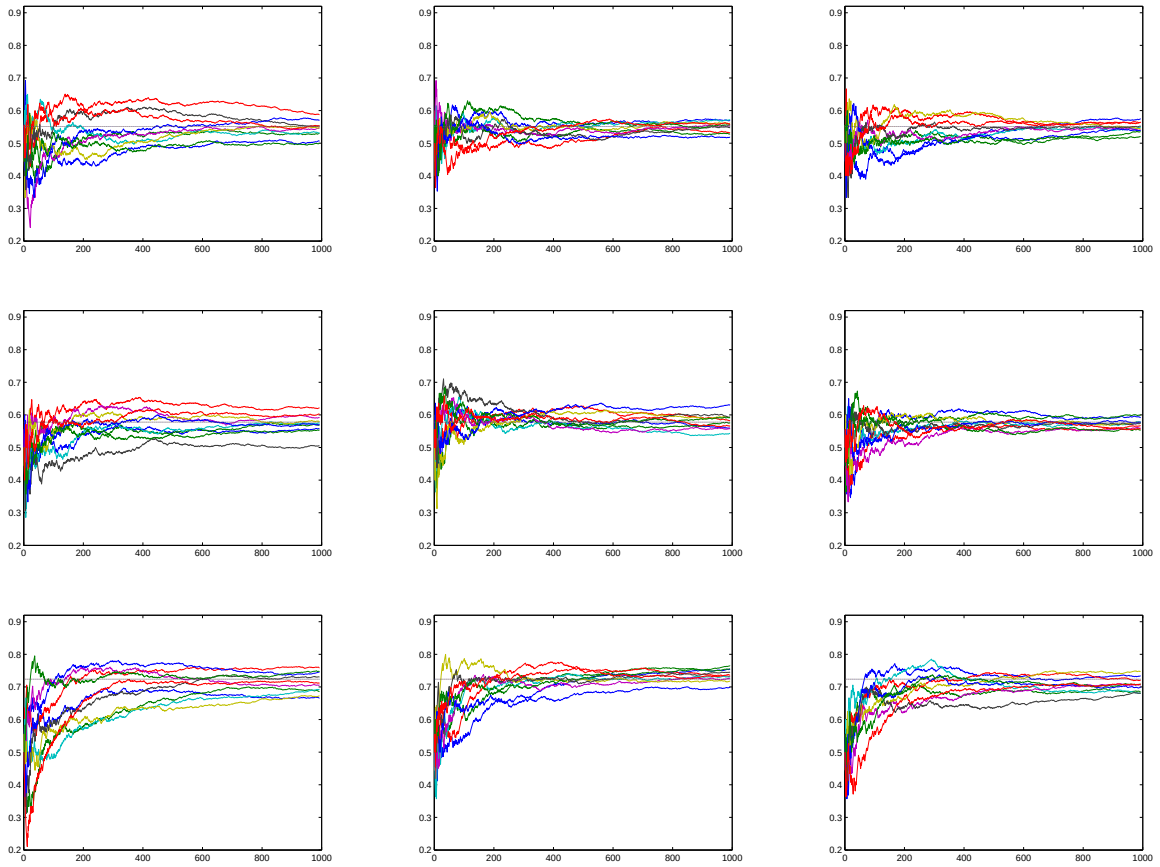

FIGURE 7. Convergence to the optimum compound target π^*_ω solving (23) for methods 1 (first column), 2 (second column) and 3 (third column), for binary responses with $\omega = \frac{1}{2}$ and $p_1 = 0.3$, $p_2 = 0.2$ (top), $p_1 = 0.65$, $p_2 = 0.4$ (middle) and $p_1 = 0.95$, $p_2 = 0.65$ (bottom).

6. THE HOMOSCEDASTIC MODEL WITH ONE CATEGORICAL COVARIATE

We now further specify (1) as follows

$$E(Y_{ik}) = \tau_k + \boldsymbol{z}_i^t \boldsymbol{\beta}\,, \quad V(Y_i) = \sigma^2 \qquad i = 1, 2, \dots n \tag{28}$$

namely the observations are homoscedastic and the response depends on the treatment and on one random categorical covariate Z with J fixed levels. The subjects will be subdivided into strata (blocks) according to the level of Z. This case was dealt with in [3]. The covariate distribution in the population is assumed to be known: $\rho_j = \Pr(Z = z_j)$ for $j = 1, \dots, J$; $\boldsymbol{\beta}$ is the vector of block effects and $\boldsymbol{z}_i$ is the indicator function of the block for the ith observation. Conditionally on the covariate and the treatment allocations, patients' responses are assumed to be independent. In the statistical literature (28) is described as a 2-factor mixed model without treatment-block interaction; in other words, the superiority of one treatment over the other (meaning $\mu_1 > \mu_2$ or vice-versa) is *uniformly* constant over the blocks. The inferential interest typically lies in testing or estimating the difference $\tau_1 - \tau_2$ as precisely as possible and $\boldsymbol{\beta}$ is usually a nuisance parameter.

Let N_j ($j = 1, \dots, J$) with $\sum_{j=1}^{J} N_j = n$ be the random size of block j after n observations and let $\boldsymbol{\pi} = (\pi_1, \dots, \pi_J)^t$ denote the vector of allocation proportions to T_1 in each block. Let $\boldsymbol{Z} = (Z_1, \dots, Z_n)^t$ be the vector of covariates for the n subjects.

From block design theory we obtain

$$Var(\hat{\tau}_1 - \hat{\tau}_2 | \boldsymbol{Z}) = \sigma^2 \left\{ n - \sum_{j=1}^{J} (2\pi_j - 1)^2 N_j \right\}^{-1},$$

so the inferential loss depends on the design through the allocation vector $\boldsymbol{\pi}$ and the block sizes. The loss is a minimum if the treatments are equally replicated within each block (for a recent discussion see [4]). The loss is random, since it depends on the block sizes which are not under the experimental control, therefore one must average over the covariate distribution. After some suitable simplifications and approximations we can let our criterion be

$$\tilde{\Psi}_I(\boldsymbol{\pi}) = E_{\boldsymbol{Z}} \left[n^{-1} \sum_{j=1}^{J} (2\pi_j - 1)^2 N_j \right] = \sum_{j=1}^{J} (2\pi_j - 1)^2 \rho_j \tag{29}$$

ranging in $[0, 1]$.

The percentage of patients assigned to the worse treatment is

$$\Pi_W(\boldsymbol{\pi}) = \frac{1}{2} + \left(\frac{1}{2} - \sum_{j=1}^{J} \pi_j \, \rho_j\right) \text{sgn}(\tau_1 - \tau_2). \tag{30}$$

We choose the compound criterion of Section 2, i.e.

$$\Phi_\omega(\boldsymbol{\pi}\ ) = \omega \, \Pi_W(\boldsymbol{\pi}) + (1-\omega) \, \tilde{\Psi}_I(\boldsymbol{\pi}). \tag{31}$$

Setting the partial derivatives with respect to π_j equal to 0 we find the set of equations

$$-\omega \text{ sgn}(\tau_1 - \tau_2) + 4(1-\omega)(2\pi_j - 1) = 0 \qquad \text{for all } j = 1, ..., J.$$

Thus the same result as (7) applies to each block so that the optimal target $\boldsymbol{\pi}^*_\omega = (\pi^*_{\omega 1}, \ldots, \pi^*_{\omega J})^t$ is given by

$$\pi^*_{\omega j} = \frac{1}{2} + \text{sgn}(\tau_1 - \tau_2) \min\left\{\frac{1}{8}\left(\frac{\omega}{1-\omega}\right)\ ,\ \frac{1}{2}\right\} \quad \text{for all } j = 1, \ldots, J. \tag{32}$$

Observe that the optimal compound target does not depend on the covariate probabilities ρ_j's and if the weight function is chosen so that $\omega < 4/5$, then $\pi^*_{\omega j} \in (0; 1)$. When $J = 1$ (no covariates), then $\tau_1 - \tau_2 = \mu_1 - \mu_2$ and (32) reduces to expression (7).

Remark 8. *This allocation is always "ethical", i.e. more subjects are assigned to the better treatment, whatever their covariate value. Since the compound optimal allocations in all the blocks are the same as (7), there is no need for further examples.*

The optimum $\boldsymbol{\pi}^*_\omega$ can be targeted by a suitable implementation of the above mentioned sequential methods adjusted for covariates by applying the same randomization function for each block. However, in [3] a different method was employed namely the randomization function

$$g_j(x; y) = \frac{y(y/x)^{\gamma_j}}{y(y/x)^{\gamma_j} + (1-y)[(1-y)/(1-x)]^{\gamma_j}} \tag{33}$$

with $\gamma_j \propto \rho_j^{-1}$ for all $j = 1, \ldots, J$, so the allocations for the profiles which may be potentially under-represented will be forced towards the optimal target.

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