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Higher order response adaptive urn designs for clinical trials with highly successful treatments

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Summary

We consider a problem of reducing the expected number of treatment failures in trials where the probability of response to treatment is close to 1 and treatments are compared based on log odds ratio. We propose a new class of urn designs for randomization of patients in a clinical trial. The new urn designs target a number of allocation proportions including the allocation proportion that yields the same power as equal allocation but significantly less expected treatment failures. The new design is compared with the doubly adaptively biased coin design, the efficient randomized adaptive design and with equal allocation. The properties of the new class of designs are studied by embedding them into a family of continuous time stochastic processes.

Keywords

Doubly adaptive biased coin design; Response adaptive design; Urn model

1. Introduction

Consider the problem of comparing two treatments in a randomized clinical trial. An issue that is central to such a trial is balancing the ethical imperative to assign more patients to the better treatment with the need to have sufficient power to compare the treatments. Response adaptive designs change allocation away from equal allocation based on responses observed so far in the trial; see Hu and Ivanova, 2004, and Hu and Rosenberger, 2006, for review. Early response adaptive designs, generalized Pólya urn (Athreya and Karlin 1968; Zhang et al., 2006), the play-the-winner rule (Zelen, 1969) and the randomized play the winner rule (Wei and Durham, 1978) were developed for comparing treatments with binary outcomes to yield “ethical” allocation in the limit, that is, to assign more patients to the better treatment. Their limiting allocation, as well as the limiting allocation for the urn design of Ivanova (2003), though “ethical”, is not optimal with respect to maximizing power of the treatment comparison. In some cases, a trial with allocation proportion that is not optimal in terms of power, requires many more subjects to achieve the same power than equal allocation. This can result in observing more failures in the trial than under equal allocation, therefore defeating the purpose of a response adaptive design to reduce the average number of failures in the trial. Other response adaptive designs such as doubly adaptive biased coin designs

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(Eisele, 1994; Hu and Zhang, 2004), and the efficient randomized adaptive design (ERADE) (Hu, Zhang and He, 2009) can target any desired allocation including the allocation that maximizes power.

An important metric of any allocation procedure is the amount of randomness it provides. In a deterministic procedure the next assignment can be predicted for sure if all previous assignments and outcomes, in case of response adaptive allocation, are known. On the other side of a spectrum is a fully randomized allocation procedure, an allocation via a fair coin, in case of equal allocation, or biased coin otherwise. We use entropy to measure randomness of the designs, a measure that has not been used before when response adaptive designs were compared. This allows making a fair comparison of adaptive procedures since deterministic procedures are more efficient in targeting the desired allocation.

Hu and Rosenberger (2003) showed that the power of treatment comparison is closely related to the variability of the allocation proportion: the higher the variability the lower the power. The variability of the allocation proportion depends on the type of allocation procedure as well as on the allocation that the design targets and the amount of randomness it provides. The urn design of Ivanova (2003) yields the lowest variability as it achieves the lower bound of the asymptotic variance of the allocation proportion (Rosenberger and Hu, 2003; Hu, Rosenberger and Zhang, 2006), so does the ERADE (Hu, Zhang and He, 2009). The doubly adaptive coin design achieves the lower bound only when the procedure is deterministic (Rosenberger and Hu, 2003). Randomness and the variability of the allocation proportion in the ERADE and the doubly adaptive coin design depends on the value of the design parameter. When several response adaptive designs that target the same allocation are compared, their corresponding design parameters can be set to provide the same amount of randomness, then the best design is the one that has the lowest variability of the allocation proportion.

Zhang et al. (2011) put the lowest variability urn design of Ivanova (2003) and other urn models into a general framework of immigrated urn models. In this paper, we generalize the design of Ivanova (2003) in a different way by allowing the change in the urn composition to depend on several previous outcomes, not only the most recent outcome. This new generalization allows targeting a large spectrum of allocation proportions, including allocations that yield good power of treatment comparison. Since the design of Ivanova (2003) yields the lowest variability of the allocation proportion the new design has low variability as well and the result has better power than competitors. The generalization, however, creates challenges in obtaining theoretical properties of the design since the new design can no longer be embedded into a family of stochastic processes unless multidimensional state space is considered.

Our motivating example is the Comparison of Arixtra in Lower Limb Superficial Vein Thrombosis with Placebo (CALISTO) trial (Decousus et al., 2010). This was a randomized trial comparing a new drug Arixtra with placebo in patients with acute symptomatic thrombophlebitis of the lower limbs. The primary efficacy outcome was a composite of death from any cause or symptomatic pulmonary embolism or symptomatic deep-vein thrombosis or symptomatic extension to the saphenofemoral junction or symptomatic

recurrence of superficial-vein thrombosis at day 47. The observed success probabilities were 99.1% in Arixtra arm and 94.1% on placebo. Similar success probabilities for placebo are often observed in other cardio-vascular trials. For example, 30-day mortality is a commonly used primary endpoint in trials comparing therapies for acute myocardial infarction, these trials yield around 93%-95% non-failure rate (Hjalmarson et al., 1985; Tebbe et al., 1998). The mortality rates are usually compared via log odds ratios. Response adaptive designs are beneficial for trials like these because they reduce the number of failures on average and increase power of treatment comparison, if the treatment is better than placebo, because when highly successful treatments are compared based on log odds ratios or relative risk the power is maximized when more patients are assigned to the better treatment (Dette, 2004).

In this paper in Section 2 we review possible target allocations for trials comparing two treatments. We introduce higher order urn designs in Section 3. Simulation results are described in Section 4. In Section 5 we re-design the CALISTO trial. Section 6 is a discussion section.

2. Optimal allocations

Consider the case where two treatments are compared. Let $N_i(n)$ be the number of subjects assigned to treatment i, $i = 1, 2$, by the time a total of n subjects have been assigned, $N_1(n) + N_2(n) = n$. The allocation proportion to treatment 1 by the time n patients have been assigned is $N_1(n)/n$. The optimal allocation proportion can be determined by using multiple-objective optimality criteria (see Jennison and Turnbull, 2000, for more details). If treatment outcomes are binary from *Bernoulli*(p_i), $0 < p_i < 1$, $q_i = 1 - p_i$, $i = 1,2$, the allocation proportion on treatment 1, $\rho_1 = \sqrt{p_1 q_1} / (\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$, Neyman allocation, minimizes the variance of $\hat{p}_1 - \hat{p}_2$. Alternatively, it minimizes the total sample size required to achieve given power if the Wald's test statistic is used to test H_0: $p_1 - p_2 = 0$. The allocation that minimizes the expected number of failures for a fixed variance of the estimate of the parameter of interest or for fixed power (Rosenberger et al., 2001) is $\rho_2 = \sqrt{p_1} / (\sqrt{p_1} + \sqrt{p_2})$. Another allocation to mention is $\rho_3 = p_1 q_1 / (p_1 q_1 + p_2 q_2)$; it yields the same power as equal allocation (see discussion of ρ_3 in Baldi Antognini and Giovagnoli, 2010). When the log odds ratio, $\log[p_1 q_2 / q_1 p_2]$, is estimated the three corresponding allocations are $\rho_1' = \sqrt{p_2 q_2} / (\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$, $\rho_2' = \sqrt{p_2 q_2} / (\sqrt{p_1 q_1} + \sqrt{p_2 q_2})$ and $\rho_3' = p_2 q_2 / (p_1 q_1 + p_2 q_2)$.

Ivanova and Rosenberger (2001) noted that response adaptive designs are most advantageous in trials with highly successful treatments, or, equivalently, trials with low probability of a bad event occurring for the following two reasons. First, in such trials treatment failure is often death (Hjalmarson et al., 1985; Tebbe et al., 1998) or severe disability (Connor et al., 1994; Simoons et al., 2002; Wallentin et al., 2003) and therefore it is most desirable to minimize the number of treatment failures. Second, if treatments are compared based on log odds ratio, the allocation that maximizes power, allocation ρ_1', assigns more patients to the better treatment when both success probabilities are higher than 0.5. In case of highly successful treatments, the allocation ρ_3' might be even a better target for a response adaptive design than allocation ρ_1' since it assigns even more patients to the better treatment and therefore further reduces the expected number of failures. For example,

the optimal allocations for success probabilities $p_1 = 0.991$ and $p_2 = 0.941$ observed in CALISTO trial are $\rho_1' = 0.717$, $\rho_2' = 0.869$ and $\rho_3' = 0.866$. The total number of failures observed in CALISTO trial was 101, 13 out of 1502 in Arixtra arm and 88 out of 1500 in placebo arm. The allocation ratio $\rho_3' = 0.866$ would have yielded 46 total failures out of 3002 patients on average if the true rates were equal to those observed in CALISTO trial, reducing the average number of failures by 55. For small sample sizes the limiting allocation ρ_3' might not be reached, still, the trial most likely will result in an allocation somewhere in $(0.5, \rho_3']$, yielding better power and reduced number of failures compared to equal allocation. Therefore ρ_3' is an ideal target allocation in trials with highly successful treatments.

3. Higher order urn designs for binary outcomes

3.1. The second order urn design for binary outcomes

We introduce the second order urn design to create an urn design that focuses on variability of the estimated treatment effect rather than the mean. As the result the new design targets allocation proportions that are optimal or nearly optimal in terms of power, such as allocation ρ_3'. Also, by modifying a low variability design from Ivanova (2003), we obtain a low variability design and therefore we expect the new design to have good power compared to competitors as variability affects power negatively (Rosenberger and Hu, 2003). The design is defined as follows:

Second order urn design—The urn contains balls of three types. Balls of types 1 and 2 represent the two treatments. Balls of type 0 are called immigration balls. Initially the urn contains $2b + a$ balls; b (≥0), balls of each treatment type and a (>0), immigration balls. Assume that j patients have been treated so far, with at least one patient assigned to each treatment. If the jth patient was assigned to treatment i, let $X^{(i)}_{N_i(j)}$ be this patient's outcome. A ball is drawn from the urn at random. If the ball is of type 0, i.e., an immigration ball, no subjects are assigned to treatment, and the ball is returned to the urn together with 2 additional balls, one of each treatment type. If a ball corresponding to treatment i is drawn, $i = 1, 2$, the next subject is assigned to treatment i and an outcome $X^{(i)}_{N_i(j)}$ is observed. If $X^{(i)}_{N_i(j)} \neq X^{(i)}_{N_i(j)-1}$, where $X^{(i)}_{N_i(j)-1}$ is the outcome of the previous subject assigned to treatment i, the ball is not returned. Otherwise, the ball is returned to the urn.

In the urn design of Ivanova (2003) the ball is not returned to the urn if there is a failure on the corresponding treatment. In the second order urn design the ball is not returned to the urn if the two most recent responses on the treatment are different. This increases the allocation to the treatment with smaller variance, thus changing the urn composition according to the variability rather than the actual outcome.

3.2. Limiting allocation proportion and variability of the second order urn design

When a response adaptive design is investigated, of most interest is the limiting distribution of the proportion of patients assigned to each treatment. To obtain this distribution for the

second order urn design, we use the technique of embedding the design into a family of continuous time stochastic processes (Athreya and Ney, 1972; Ivanova et al., 2003). Let $\boldsymbol{Z}_m = (Z_{m0}, Z_{m1}, Z_{m2})$ denote the urn composition after m consecutive draws, including draws of immigration balls, where Z_{m0} is the number of immigration balls and Z_{mi} is the number of balls of treatment type i, $i = 1,2$. Define the continuous time analog of the urn as follows. Let τ_m be the time of the mth draw, and $\tau = 0$. Given the urn composition after m draws, $\boldsymbol{Z}(\tau_m) = (Z_{m0}, Z_{m1}, Z_{m2})$, generate three independent random variables $\boldsymbol{V}_0$, $\boldsymbol{V}_1$, and $\boldsymbol{V}_2$, such that $\boldsymbol{V}_i$ has exponential distribution with mean $1 / Z_{mi}$, $i = 0,1, 2$. Let $T_{m+1} = \min(\boldsymbol{V}_0, \boldsymbol{V}_1, \boldsymbol{V}_2)$ and define $\tau_{m+1} = \tau_m + T_{m+1}$. If $T_{m+1} = \boldsymbol{V}_i$ the drawn ball is of type i. The urn composition after $m + 1$ draws, $\boldsymbol{Z}(\tau_{m+1})$, is obtained as described in Section 3.1. The stochastic processes $\{\boldsymbol{Z}_m; m = 0,1,2,\ldots\}$ and $\{\boldsymbol{Z}(\tau_m); m = 0,1,2,\ldots\}$ have the same transition probabilities and therefore are equivalent. It can be shown that $\tau_m \to \infty$ almost surely (Athreya and Ney, 1972). We define $\boldsymbol{Z}(t)$, $t > 0$, to be the right continuous version of $\boldsymbol{Z}(\tau_m)$, $\boldsymbol{Z}(t) = (Z_0(t), Z_1(t), Z_2(t))$. This defines $Z_i(t)$, $i = 0,1,2$, as the number of balls of type i at time t. See Athreya and Ney (1972), Ivanova et al. (2000), Ivanova (2003) and Ivanova (2006) for more details on embedding a discrete type stochastic process into a continuous type process. As a result, the urn design can be described by using the notion of continuous time which is a useful mathematical construct not related to the real time in the medical experiment. Let $U_i(t)$ be the number of draws of a ball of treatment type i resulting in a success on treatment i, and $Y_i(t)$ be the number of draws of a ball of type i resulting in a failure on treatment i, so that the number of trials on the ith treatment is $N_i(t) = U_i(t) + Y_i(t)$, $i = 1,2$. Let $I(t)$, the immigration process, be the number of draws of balls of type 0, immigration balls. By construction $Z_i(t) = Z_i(0) + I(t) - Y_i(t)$. The total number of draws of a ball of treatment type i, $N_i(t)$ is of most interest to us, while the number of balls in the urn, $Z_i(t)$, is the quantity that defines the process. The stochastic processes literature focuses on $Z_i(t)$. Ivanova et al. (2000) extended the technique from Cox and Miller (1965, p. 265) to obtain the differential equation for the joint probability generating functions. To describe the behavior of $N_i(t)$, we will obtain its joint probability generating function with the number of balls in the urn, $Z_i(t)$, $G^{(i)}(,t\ z\ w) = E\ (z^{Zi(t)}w^{Ni(t)})$. Since the two most recent responses are used, consider the generating function $G_0^{(i)}(t, z, w)$ describing the behavior of the process corresponding to treatment i when the preceding state was 0, the penultimate outcome on treatment i was a failure, and $G_1^{(i)}(t, z, w)$ describing the behavior of the process when the preceding state is 1, the penultimate response on treatment i was a success. Then we have

$$\begin{aligned} G^{(i)}(t,z,w) &= E\left(z^{z_i(t)}w^{N_i(t)}\right) \\ &= E\left(z^{z_i(t)}w^{N_i(t)} \mid \text{penultimate outcome was a failure}\right) q_i + E\left(z^{z_i(t)}w^{N_i(t)} \mid \text{penultimate outcome was}\right. \\ &= q_i G_0^{(i)}(t,z,w) + p_i G_1^{(i)}(t,z,w). \end{aligned}$$

Using backward equations, the following system of equations is obtained (see Appendix I for more details):

$$\begin{aligned}\frac{\partial G_0^{(i)}(t,z,w)}{\partial t}&=\frac{\partial G_0^{(i)}(t,z,w)}{\partial z}\left(q_i wz-z\right)+\frac{\partial G_1^{(i)}(t,z,w)}{\partial z}q_i w+a\left(z-1\right)G_0^{(i)}\left(t,z,w\right)\\ \frac{\partial G_1^{(i)}(t,z,w)}{\partial t}&=\frac{\partial G_1^{(i)}(t,z,w)}{\partial z}\left(p_i wz-z\right)+\frac{\partial G_0^{(i)}(t,z,w)}{\partial z}p_i w+a\left(z-1\right)G_1^{(i)}\left(t,z,w\right).\end{aligned} \quad (1)$$

Initial and boundary conditions are $G_0^{(i)}(0,z,w)=G_1^{(i)}(0,z,w)=z$ and $G(i)(t, 1, 1) = 1$, $i = 1, 2$, with $t \geq 0$, $|z| \leq 1$, and $|w| \leq 1$.

The quantity $N_i(t) / [N_1(t) + N_2(t)]$ is the allocation proportion to treatment i by time t. By construction, it is also the allocation proportion to treatment i among the first $J(t)$ patients in the embedded urn process, where $J(t) = N_1(t) + N_2(t)$. As $t \to \infty$ therefore, if both $J(t) \to \infty$ and $N_i(t) / [N_1(t) + N_2(t)]$ converges in probability to a limit, then this limit is equal to the limiting allocation proportion in the urn process. We now sketch a demonstration that this is indeed so. For more details, see Ivanova et al. (2000); Ivanova (2003).

The limit of the allocation proportion can be computed (Ivanova, 2003) by first obtaining

$$E\left\{N_i\left(t\right)\right\}=\left.\frac{\partial\left\{log\quad G^{(i)}\left(t,1,w\right)\right\}}{\partial w}\right|_{w=1}.$$

It might not be possible to obtain the closed form solution of the system of equations (1) except for special cases. Using characteristic function approach (Ivanova et al., 2000) we can show that $\lim_{t\to\infty} E\{N_i(t) / t\}$ is $a / (2p_iq_i)$, where the limit is in probability, and that $N_i(t) \to \infty$, i=1,2, almost surely as $t \to \infty$. Hence $J(t) \to \infty$ almost surely, as required. Next, similarly to Ivanova (2003), the limit in probability of the allocation proportion is

$$lim_{t\to\infty}\left\{\frac{N_1\left(t\right)}{N_1\left(t\right)+N_2\left(t\right)}\right\}=\frac{a\,/\,\left(2p_1q_1\right)}{a\,/\,\left(2p_1q_1\right)+a\,/\,\left(2p_2q_2\right)}=\frac{p_2q_2}{p_1q_1+p_2q_2},$$

which is $\rho_3^{'}$ defined in Section 2. This demonstrates that the limiting allocation in the embedded urn process is $\rho_3^{'}$.

The variability can be assessed by computing

$$\begin{aligned}var\left\{N_i\left(t\right)\right\}&=\frac{d}{dw}\left[w\frac{d\left\{log\,G^{(i)}(t,1,w)\right\}}{dw}\right]\Bigg|_{w=1},\\ cov\left\{N_1\left(t\right),\,N_2\left(t\right)\right\}&=\frac{\partial}{\partial w_1}\frac{\partial}{\partial w_2}log\,G^{(1,2)}\left(t,1,w_1,w_2\right)\Bigg|_{w_1=w_2=1},\end{aligned}$$

where $G^{(1,2)}(t, 1, w_1, w_2)$ is a joint function for $N_1(t)$ and $N_2(t)$ (see Ivanova, 2006, for details). It was not possible to obtain the closed form expressions for $var\{N_1(t)\}$, $varN_2(t)$ and $cov\{N_1(t), N_2(t)\}$ for given t and as $t\to\infty$, so we resorted to numerical computations.

3.3. Higher order urn designs

In Section 3.1 we introduced the design that is an extension of the low variability design from Ivanova (2003) and uses two most recent responses instead of one response as in the original Ivanova design. In this section we extend the design further by using three or more responses. This extension creates designs that target an even wider range of allocation proportions and converge faster than the second order urn design while keeping variability low as before.

To describe this extension we first note that the second order design defined in Section 3.1 can be alternatively defined using the estimate of success probability obtained from the two most recent observations. The estimate $\hat{p}_i = \left(X^{(i)}_{N_i(j)} + X^{(i)}_{N_i(j)-1}\right)/2$, i =1, 2, can take on three possible values 0, 1/2 and 1. The ball of type i is not returned if $\hat{p}_i$ = 0.5. Similarly, in the kth order urn design, the estimate of success rate is based on the k most recent responses: $\hat{p}_i = \sum_{m=1}^{k} X^{(i)}_{N_i(j)-m+1}/k$. Let an integer α be such that $k = 2a$, if k is even, or $k = 2a + 1$, if k is odd. Consider the kth order design where the ball is not returned if $\hat{p}_i = \alpha/k$ or $\hat{p}_i = 1 - \alpha/k$, that is, the ball is not returned if the estimate of success rate is the closest possible to 0.5. The probability of not returning the ball is $Q_i = C^k_\alpha p_i^\alpha q_i^\alpha$ if $k = 2a$, or $Q_i = C^k_\alpha p_i^{\alpha+1} q_i^\alpha + C^k_\alpha p_i^\alpha q_i^{\alpha+1} = C^k_\alpha p_i^\alpha q_i^\alpha (p_i + q_i) = C^k_\alpha p_i^\alpha q_i^\alpha$ if $k = 2a + 1$. Here $C^k_\alpha = k!/[\alpha!(k-\alpha)!]$ is a binomial coefficient with $C^k_\alpha = 0$, if $\alpha < 0$ or $\alpha > k$. The limiting allocation proportion for this urn design (Ivanova, 2003) is equal to $Q_2/(Q_1 + Q_2) = p_2^\alpha q_2^\alpha/(p_1^\alpha q_1^\alpha + p_2^\alpha q_2^\alpha) = \rho(\alpha)$. For example, when k = 3 (so that a = 1) the limiting allocation proportion is $\rho(a = 1) = p_2 q_2/(p_1 q_1 + p_2 q_2) = \rho_3'$, when k = 4, the allocation is $\rho(\alpha = 2) = p_2^2 q_2^2/\left(p_1^2 q_1^2 + p_2^2 q_2^2\right)$. For $p_1 > p_2$ and $a > \beta$, $\rho(a) > \rho(\beta)$, therefore for all $\alpha > 1$ $\rho(a)$ is closer to 1 than $\rho(1) = \rho_3'$. Allocations $\rho(a)$ for $\alpha > 1$ might be desirable for trials with the goal of selecting the best treatment, however, as was discussed in Section 2, the power under allocations $\rho(a)$ with $\alpha > 1$ is lower than under ρ_3' or under equal allocation.

With the use of a biased coin the kth order urn design can be made to target the desirable allocation ρ_3'. The kth order urn design with biased coin, k = 4, 5…, that targets ρ_3' is described as follows. If m successes were observed in the last k patients assigned to treatment i, i =1, 2, the ball of type i is not returned if 1) the estimated success probability from the last k patients assigned to treatment i is away from 0 or 1, that is, m = 1,…, k−1; and 2) a biased coin with probability of heads equal to $C^k_\alpha C^{k-2}_{m-1}/\left(C^{k-2}_{\alpha-1} C^k_m\right)$ lands heads. To show that this design targets ρ_3', we first compute the probability of not returning the ball

$$\begin{aligned} Q_i &= \sum_{m=1}^{k-1} \frac{C^k_\alpha}{C^{k-2}_{\alpha-1}} \frac{C^{k-2}_{m-1}}{C^k_m} C^k_m p_i^m q_i^{k-m} = \frac{C^k_\alpha}{C^{k-2}_{\alpha-1}} p_i q_i \sum_{m=1}^{k-1} C^{k-2}_{m-1} p_i^{m-1} q_i^{k-m-1} \\ &= \frac{C^k_\alpha}{C^{k-2}_{\alpha-1}} p_i q_i \sum_{m'=0}^{k-2} C^{k-2}_{m'} p_i^{m'} q_i^{k-2-m'} = \frac{C^k_\alpha}{C^{k-2}_{\alpha-1}} p_i q_i (p_i + q_i)^{k-2} = \frac{C^k_\alpha}{C^{k-2}_{\alpha-1}} p_i q_i. \end{aligned}$$

Therefore the limiting allocation is equal to $Q_2/(Q_1 + Q_2) = p_2q_2/(p_1q_1 + p_2q_2) = \rho_3'$. For example, when $k = 4$, the possible values for ρ_1' are 0, 1/4, 1/2, 3/4, and 1. According to the design described above, the ball is not returned if $\rho_1' = 1/2$; or if $\rho_1' = 1/4,3/4$ and a biased coin with the probability of heads equal to 3/4 lands heads. When $k = 5$, the ball is not returned if $\rho_1' = 2/5, 3/5$; or if $\rho_1' = 1/5, 4/5$ and a biased coin with the probability of heads equal to 2/3 lands heads.

4. Comparison with competing designs

In this section we compare the new urn designs with the doubly adaptive biased coin design (Hu and Zhang, 2004) and the efficient randomized adaptive design (Hu, Zhang and He, 2009).

The doubly adaptive biased coin design (Hu and Zhang 2004) allocates patient j to treatment i with probability $g\left(N_i\left(j\right)/\left(j-1\right),\hat{\rho}\right)$, where $\hat{\rho}$ is the target proportion estimated from the data. We use the choice of g from Hu and Zhang (2004):

$$\begin{aligned} g\left(x,\rho\right) &= \frac{\rho(\rho/x)^{\gamma}}{\rho(\rho/x)^{\gamma}+(1-\rho)[(1-\rho)/(1-x)]^{\gamma}}, \\ g\left(0,\rho\right) &= 1, \\ g\left(1,\rho\right) &= 0. \end{aligned}$$

Here γ is a design parameter controlling the amount of randomization in the design. Let $\rho(p_1, p_2)$ be the target allocation proportion as a function of p_1 and p_2, for example, $\rho\left(p_1,p_2\right) = \sqrt{p_2q_2}/\left(\sqrt{p_1q_1}+\sqrt{p_2q_2}\right)$ for inverse Neyman allocation. Hu and Zhang (2004) give the following formula for the asymptotic variance, ω^2, of $N_1(n)/n$

$$\begin{aligned} \omega^2 &= \frac{\omega_1^2}{1+2\gamma}+\frac{2(1+\gamma)}{1+2\gamma}\omega_2^2, \text{ where} \\ \omega_1^2 &= \rho\left(p_1,p_2\right)\left[1-\rho\left(p_1,p_2\right)\right] \text{ and} \\ \omega_2^2 &= \left(\frac{\partial\rho(p_1,p_2)}{\partial p_1}\right)^2\frac{p_1q_1}{\rho(p_1,p_2)}+\left(\frac{\partial\rho(p_1,p_2)}{\partial p_2}\right)^2\frac{p_2q_2}{1-\rho(p_1,p_2)}. \end{aligned}$$

When $\gamma = 0$, the design is fully randomized, and the variance is $\omega_1^2+2\omega_2^2$; when $\gamma = +\infty$ the design is deterministic, the variance is ω_2^2 and is equal to the lower bound of the asymptotic variance. Hu and Rosenberger (2005) recommended using the design with $\gamma = 2$.

The ERADE (Hu, Zhang and He, 2009) is a generalization of Efron's coin which attains the lower bound of the asymptotic variance and can target any desirable allocation. The ERADE requires specifying a design parameter π, $0 \le \pi < 1$, that reflects the degree of randomization, with larger values of π corresponding to more randomization and variability. The design is defined as follows. As before, $\hat{\rho}$ is the estimated target allocation for treatment 1. Then the next patient is assigned to treatment 1 with probability $\hat{\rho}\pi$ if the actual allocation to treatment 1 exceeds $\hat{\rho}$; with probability $\hat{\rho}$ if the actual allocation is equal to the estimated target allocation; with probability $1-(1-\hat{\rho})\pi$ if the actual allocation is below the estimated target allocation. Hu, Zhang and He (2009) studied the choice of π and found that the

simulated results of $\pi = 1/8$ and 1/4 were very similar to the results of $\pi = 1/2$ in terms of allocation proportion and its variability, and the ERADE with $\pi = 3/4$ has a slightly larger variability than others. They recommended using π in [0.4, 0.7]. Since the ERADE with $\pi =$ 0.5 performed very similar to lower values of ERADE we used the ERADE with $\pi = 0.5$.

We compared designs based on variability of allocation proportion and randomness. Randomness was quantified by summing entropy of the allocation distribution for each assignment, $-\sum_{j=1}^{N} \xi_j \quad \log(\xi_j)$, where ξ_j is the probability of being assigned to treatment 1 after $(j - 1)$ patients have been assigned. For a given p_1 and p_2, the sample size, N, used for entropy calculations was that which yields 80% power with a two-sided type I error rate of 0.05 for testing based on the log odds ratio. For the adaptively biased coin design $\xi_j = g(N_1(j)/(j-1), \hat{\rho})$. In the case of the third order urn design, ξ_j is equal to $\sum_{m=0}^{\infty} (z_1(j) + m) \left\{ \prod_{k=0}^{m} (z_1(j) + z_2(j) + 1 + 2k) \right\}^{-1}$, where $z_i(j)$ is the number of balls of type j in the urn right after the most recent treatment (non-immigration) ball was chosen, and the sum is over the number of immigration balls m to be drawn before a treatment ball is drawn. The product in the denominator is the probability that $m - 1$ immigration balls are chosen before $z(j)$ is finally chosen. We have not been able to obtain a closed form for the sum. Noting that the sum of all terms after the mth term is less than the mth term (see Appendix II) it is easy to obtain the numerical value for the sum with any degree of accuracy. We computed the sum within 10^{-14} of the true value.

First, we compare the asymptotic variance of the second and third order urn designs with the lower bound of the asymptotic variance of designs that target ρ_3' and the asymptotic variance of the doubly adaptive biased coin design with $\gamma = 2$. Fig. 1 displays the asymptotic variances for $p_2 = 0.90$ and p_1 in [0.90, 0.99]. Even though the design from Ivanova (2003) achieves the lower bound of the asymptotic variance, the higher order urn designs do not, but their variances are very close to the lower bound and are significantly smaller than those of the biased coin design with $\gamma = 2$.

Second, for each (p_1, p_2), we computed the sample size required to achieve 80% power in a trial with equal allocation. Then we compared response adaptive designs using these sample sizes. We compared the second and third order urn designs to the adaptively biased coin design with $\gamma = 2$ and ERADE with $\pi = 0.5$ for values of p_1 and p_2 greater than 0.5 based on the variance of the allocation proportion and on the amount of randomness the designs provide. The regions of (p_1, p_2) sample space where the third order urn design has higher entropy, which is more desirable, are marked with vertical lines in Fig. 2. Elements of (p_1, p_2) space where the asymptotic variance for the third order urn design was smaller are marked with horizontal lines in Fig. 2. In Section 2 we proposed ρ_3' as the target allocation in a trial where treatment comparison is based on the log odds ratio. The first row of Fig. 2 shows the comparison with the adaptively biased coin design and the ERADE targeting ρ_3', the second row targeting ρ_1'. Fig. 2 shows that the third order urn design performs well against the adaptively biased coin design and the ERADE targeting ρ_3' in about half of the 2-dimensional region of (p_1, p_2). When the coin design and the ERADE target ρ_1' the region

where the new design is better is smaller, however, the advantage of the proposed design still holds for trials where highly successful treatments are compared.

5. Example: re-designing CALISTO trial

The proposed approach is illustrated by re-designing the CALISTO trial (Decousus et al., 2010). The total sample size in the trial was 3002 patients with 1502 patients assigned to Arixtra and 1500 to placebo. The sample size of 3000 was chosen because it yields the power of 87% to detect a 2 percentage point absolute increase in incidence of events at the two-sided 0.05 level of significance using Fisher's exact test, provided the incidence in the placebo group is no greater than 2%. Observed success probabilities were $p_1 = 0.991$ in the Arixtra arm and $p_2 = 0.941$ in placebo arm. For $p_1 = 0.991$ and $p_2 = 0.941$, the optimal allocations are $\rho_1' = 0.717$, which minimizes the sample size given power, $\rho_2' = 0.869$, which minimizes the expected number of failures given power, and $\rho_3' = 0.866$, the allocation that yields the same power as equal allocation but less treatment failures. The limiting allocation for our proposed urn design coincides with ρ_3'. For the success probabilities in the CALISTO trial both the coin design and the ERADE perform better when targeting ρ_1', therefore we describe simulation results for these two designs for ρ_1' target only. To redesign the CALISTO trial we first found the values of parameters γ in the coin design and π in the ERADE design that yield the same randomness, measured by the total entropy, as the third order urn design. These parameters were $\gamma = 0$ for the coin design and $\pi = 0.28$ for the ERADE. Then trials with assignments by the coin design and the ERADE were simulated. Results are presented based on 5000 simulated trials. The simulation study was repeated with recommended values $\gamma = 2$ and $\pi = 0.5$ yielding similar conclusions. To simulate the CALISTO trial we resampled from CALISTO data knowing that 13 out of 1502 failures were observed in Arixtra arm and 88 out of 1500 in placebo arm. Results when data were simulated from Bernoulli distribution with success probabilities $p_1 = 0.991$ and $p_2 = 0.941$ were very similar. If equal allocation is used and true probabilities are $p_1 = 0.991$ and $p_2 = 0.941$, 536 subjects total are required to achieve 90% power in a two-sided test with the type I error rate of 0.05. As the sample size in the CALISTO trial was much larger than needed we re-designed the trial as a two-stage trial with the Pocock boundary (Pocock, 1977) to allow stopping early for efficacy after outcomes from the first 1500 patients were observed. In fact, all trials were stopped for efficacy after 1500 patients essentially yielding a single stage trial with a total sample size of 1500. The average number of failures and the 5th and 95th percentiles were 33 (25, 42) for the coin design, 34 (28, 41) for ERADE, 30 (26, 34) for the urn design and 50 (43, 59) for equal allocation. All response adaptive designs dramatically reduced the total expected failures with the new urn design yielding the smallest number of failures.

Fig. 3 shows power curves in the informative region of total sample sizes, between 300 and 600, for the third order urn design, the ERADE, and equal allocation. Power for the adaptively biased coin design is inferior and is not shown. As seen from Fig. 3, the proposed urn design has better power than equal allocation and the ERADE. Better power for the urn design is the result of low variability of the allocation proportion (Fig. 4). The average

allocation proportion and its 25th and 75th percentiles (Fig. 4) show that the allocation proportion of the doubly adaptive coin design and the ERADE converges to the limiting proportion quickly, but that the variability of the allocation proportion is high. For example, for the total sample size of 300, the allocation proportion in 10% of the trials is 90:10 or more extreme when the target is, in fact, $\rho_1' = 0.717$. This makes the design more sensitive to time trends and to have low power in case multiple interim analyses are performed. Though the urn design converges more slowly, it is far less variable.

We also performed simulations with delayed response. As shown by Bai, Hu and Rosenberger (2002) the asymptotic properties of response adaptive designs under delay in outcome are the same as without a delay unless the delay is substantial and as long as adaptations are done frequently. We assumed that the data from the first patient were only available when the kth patient was enrolled, the data from the second patient were available when the (k+1) patient was enrolled etc. For example, if $k \geq 1500$ in a trial with 1500 patients total, no data are available to modify the allocation proportion. If no data were available to modify the allocation proportion patients were randomized by flipping a fair coin. A delay with $k = 500$ yielded 39, 39 and 38 failures on average for the coin design, the ERADE and the urn design with fewer failures observed on average than 50 failures under equal allocation. Significant delay of $k = 1000$ in a trial of 1500 yielded 44, 44 and 45 failures on average for the three adaptive designs, only slightly fewer failures than under equal allocation with faster converging coin and ERADE designs now performing better than the urn design. Note that if the adaptations of the allocation proportion are only performed once or twice during the trial, the proposed urn design is not suitable and the adaptively biased coin or the ERADE should be used. Both the coin design and the ERADE estimate the success probabilities using all available data and compute the desirable allocation proportion.

6. Conclusions

The doubly adaptively biased coin design and ERADE estimate success probabilities from all available data, then estimate the target allocation which is a function of these probabilities and therefore can target any allocation proportion that is a function of success probabilities. Both designs converge rapidly to the target, however, the variability of the allocation proportion is high as well. The proposed higher order urn design does not estimate success probabilities from all data but rather takes them into account indirectly using only the most recent data. It, therefore, converges to the target allocation more slowly, however, is far less variable. In the example considered, the third order urn design does not result in extreme allocations and yields higher power than the doubly adaptive coin design, the ERADE and equal allocation. Another advantage of the proposed urn designs is that one does not have to know the most recent estimates of the treatments' success probabilities p_1 and p_2. For the third order urn design, for example, one only needs to know if there were any failures among the most recent 3 responses. Therefore, if data used for a recent adaptation accidently become known to investigators, they will not know the most recent estimates of p_1 and p_2.

In the CALISTO trial example where two highly successful treatments were compared, all three response adaptive designs yielded substantial savings in failures compared to equal allocation. The proposed third order urn design and the ERADE resulted in similar or better power than equal allocation. Therefore, it is worth considering response adaptive designs as a design option for trials with highly successful treatments.

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APPENDIX I

Though we have two processes corresponding to the two treatment arms, it is sufficient to describe the behavior of a Markov process corresponding to a single treatment arm with success rate of p, $q = 1 - p$. In similar derivations in Ivanova et al. (2001) and Ivanova (2003) the state that the process is in was a function of the number of balls currently in the urn. In the second order urn, the state that the process is in is determined by the response of the previous patient and the number of balls currently in the urn. The initial urn contains one ball of each type. Assume that one patient has been already treated and response observed. If the response was a success, $X_1 = 1$, the Markov process starts at the state (1,1), if response was a failure, $X_1 = 0$, the Markov process starts at the state (0,1). Assume that the process is at the state $(0, m)$, $m > 0$, at time t. The following transitions are possible in time Δt:

$$\begin{aligned}(0,m) &\to (0,m-1) \text{ with rate } mp\Delta t\\ (0,m) &\to (0,m) \text{ with rate } mq\Delta t\\ (0,m) &\to (0,m+1) \text{ with rate } a\Delta t\end{aligned}$$

Similarly, if the process is in the state $(1, m)$, $m > 0$, at time t, the transitions in time Δt are:

$$\begin{aligned}(1,m) &\to (1,m-1) \text{ with rate } mq\Delta t\\ (1,m) &\to (1,m) \text{ with rate } mp\Delta t\\ (1,m) &\to (1,m+1) \text{ with rate } a\Delta t\end{aligned}$$

Let $p_{0,m}(t)$ equal the probability of being at state $(0, m)$ at time t, and $p_{1,m}(t)$ equal the probability of being at state $(1, m)$ at time t. To obtain backward equations we consider all possible ways to get to states $(0,m)$ and $(1,m)$ by time t:

$$\begin{aligned}&(1,m+1) \to (0,m) \text{ with rate } (m+1)\,q\Delta t,\\ &(0,m-1) \to (0,m) \text{ with rate } a\Delta t,\\ &(0,m) \to (0,m) \text{ with rate } 1+mq\Delta t - m\Delta t - a\Delta t,\\ &(0,m+1) \to (1,m) \text{ with rate } (m+1)\,p\Delta t,\\ &(1,m-1) \to (1,m) \text{ with rate } a\Delta t,\\ &(1,m) \to (1,m) \text{ with rate } 1+mp\Delta t - m\Delta t - a\Delta t.\end{aligned} \quad (2)$$

Define generating functions

$$G_0(t,z)=\sum_{m=0}^{\infty}p_{0,m}(t)\,z^m,\quad G_1(t,z)=\sum_{m=0}^{\infty}p_{1,m}(t)\,z^m. \quad (3)$$

The system of partial differential equations (1) and its initial and boundary conditions are obtained from (2) and (3).

APPENDIX II

Define $a_{j,m}=\{z_1(j)+m\}\left\{\prod_{k=0}^{m}(z_1(j)+z_2(j)+1+2k)\right\}^{-1}$, $m \geq 0$. We would like to show that $\sum_{k=m+1}^{\infty}a_{j,k} \leq a_{j,m}$. We first show that, $a_{j,m+1} / a_{j,m} \leq 0.5$. This ratio is

$$\begin{aligned}\frac{a_{j,m+1}}{a_{j,m}} &= \frac{z_1(j)+m+1}{\prod_{k=0}^{m+1}\{z_1(j)+z_2(j)+1+2k\}}\left\{\frac{z_1(j)+m}{\prod_{k=0}^{m}\{z_1(j)+z_2(j)+1+2k\}}\right\}^{-1}\\ &= \frac{z_1(j)+m+1}{\{z_1(j)+z_2(j)+1+2(m+1)\}\prod_{k=0}^{m}\{z_1(j)+z_2(j)+1+2k\}}\left\{\frac{z_1(j)+m}{\prod_{k=0}^{m}\{z_1(j)+z_2(j)+1+2k\}}\right\}^{-1}\\ &= \frac{\frac{z_1(j)+m+1}{\{z_1(j)+m\}\{z_1(j)+z_2(j)+2m+3\}}}{\frac{1}{(z_1(j)+z_2(j)+2m+3)}+\frac{1}{(z_1(j)+m)(z_1(j)+z_2(j)+2m+3}} \leq \frac{1}{4}+\frac{1}{4}=\frac{1}{2},\end{aligned}$$

because all terms are nonnegative and $z_1(j) + m \geq 1$.

The geometric sequence 0.5^n has the property that the sum of all terms beyond the mth term is equal to the mth term. Then, $a_{j,m+k} < (a_{j,m})(0.5)^k$ and therefore $\sum_{k=m+1}^{\infty}a_{j,k} \leq a_{j,m}$.

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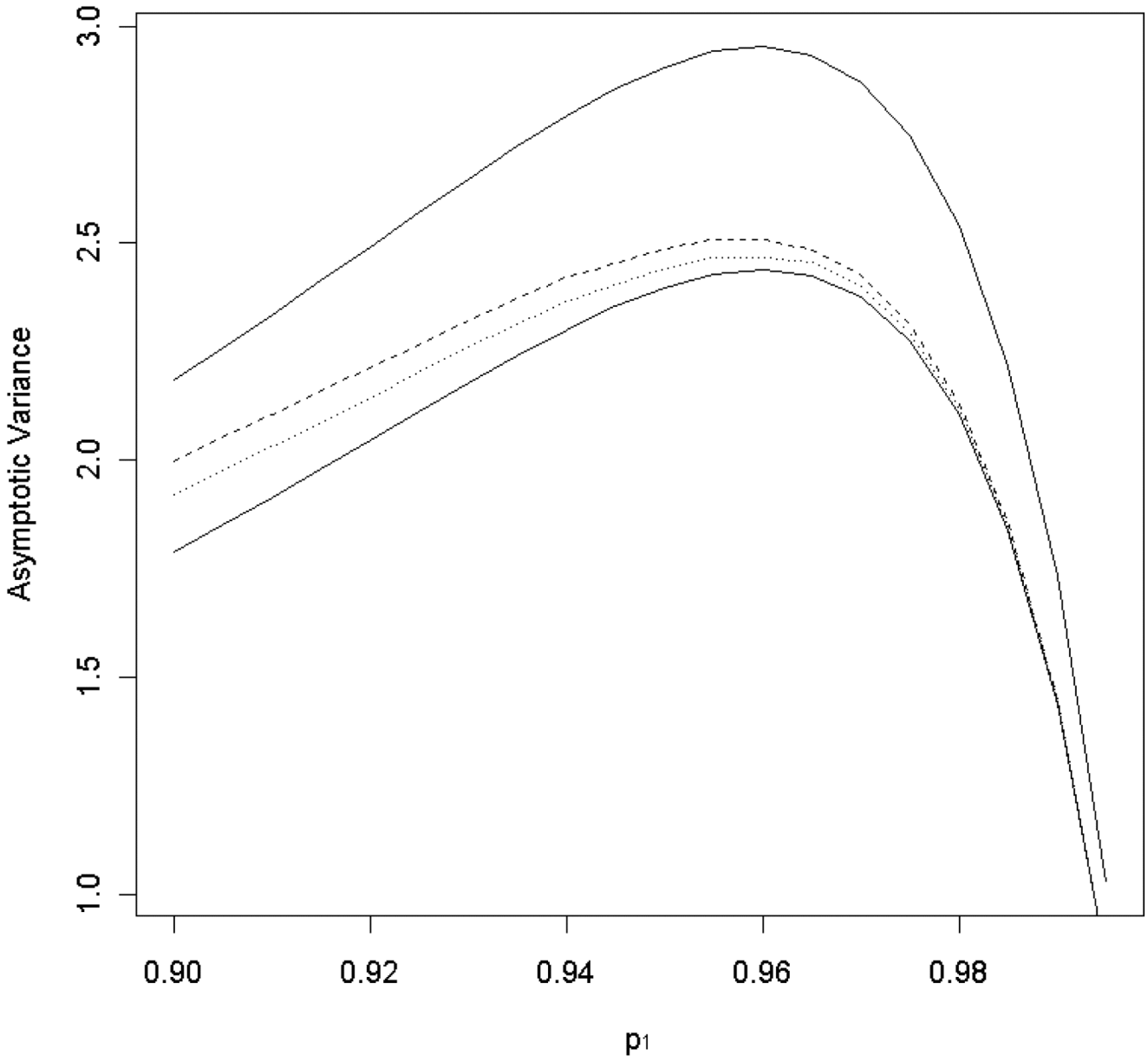

Fig. 1.

The asymptotic variance of the second order urn design (dashed line), the third order urn design (dotted line) and the doubly adaptive biased coin design with parameters $\gamma = 2$ (upper solid line) and $\gamma = \infty$ (lower solid line). Success rate $p_2 = 0.9$.

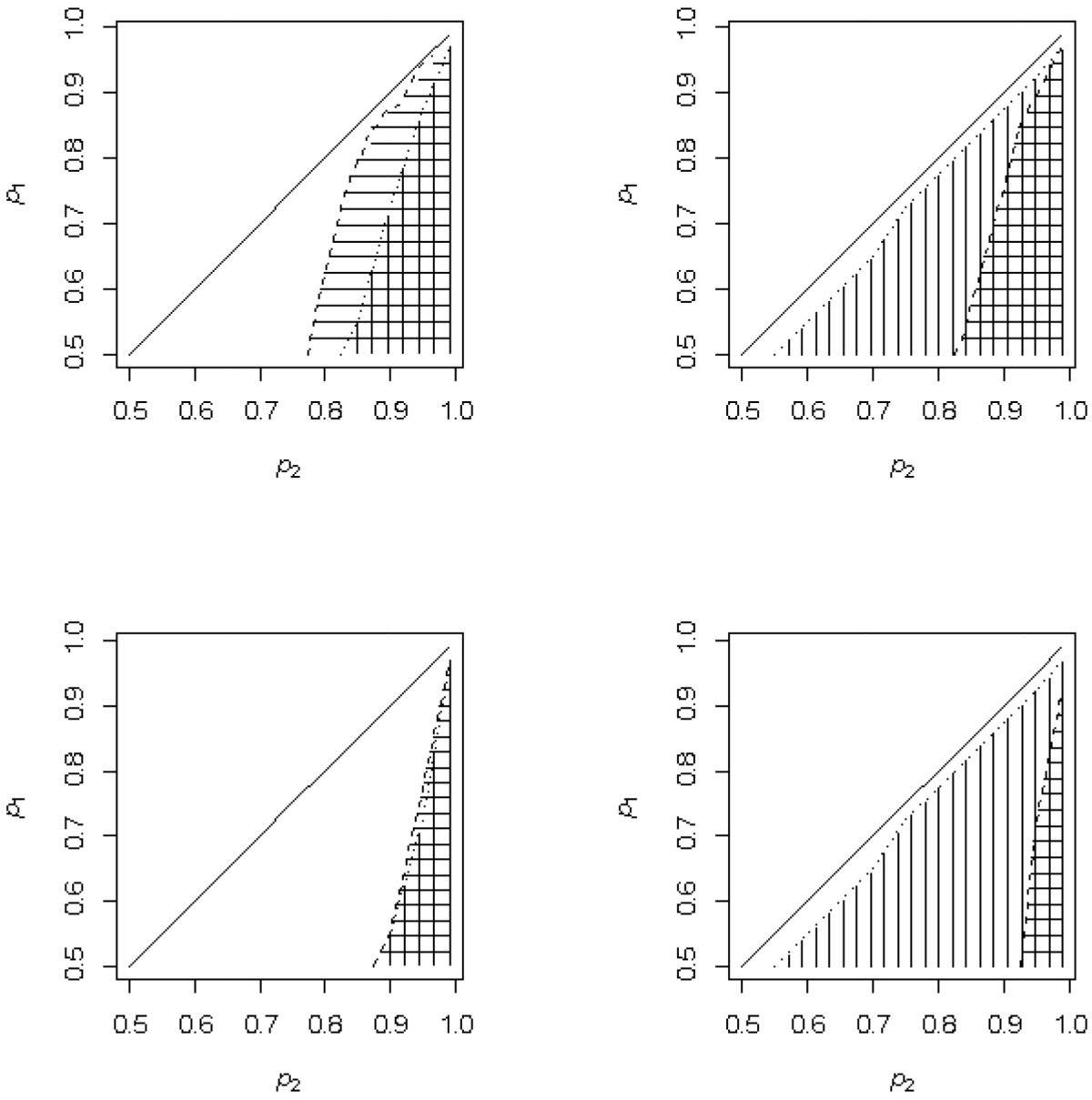

Fig. 2.

Range of success probabilities p_1 and p_2 where third order urn design has smaller asymptotic variance (horizontal lines) and higher entropy (vertical lines) than the doubly adaptive coin design with $\gamma = 2$ (left panel) or ERADE with $\pi = 0.5$ (right panel). The diagonal line is the boundary of the sample space. The first row is for the coin design and ERADE targeting ρ_3', the second for ρ_1'.

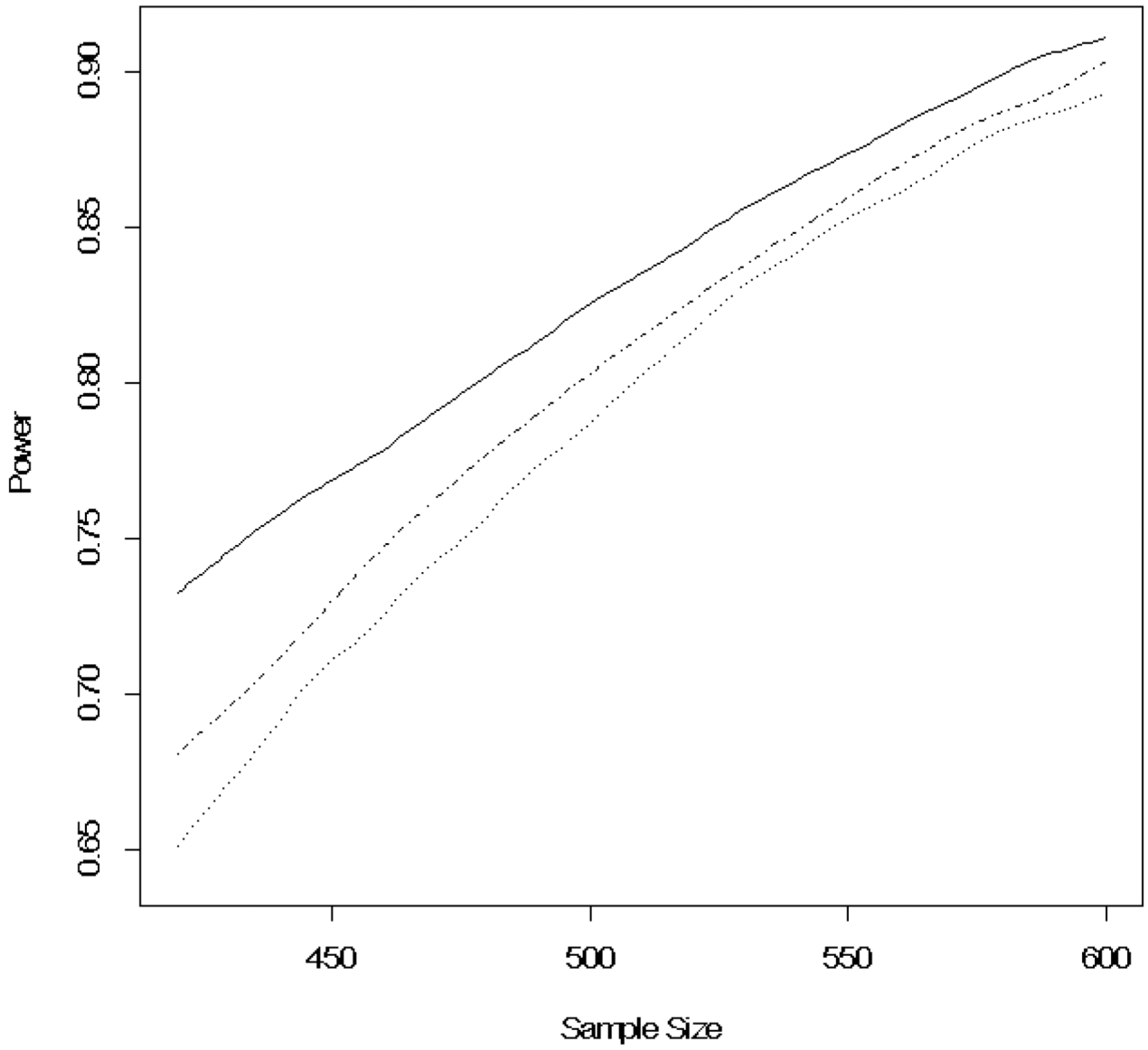

Fig. 3.

Power for the CALISTO trial with $p_1 = 0.991$ and $p_2 = 0.941$ for third order urn design (solid line), the equal allocation (dotted-dashed line) and the ERADE with $\pi = 0.28$ targeting ρ_1' (dotted line).

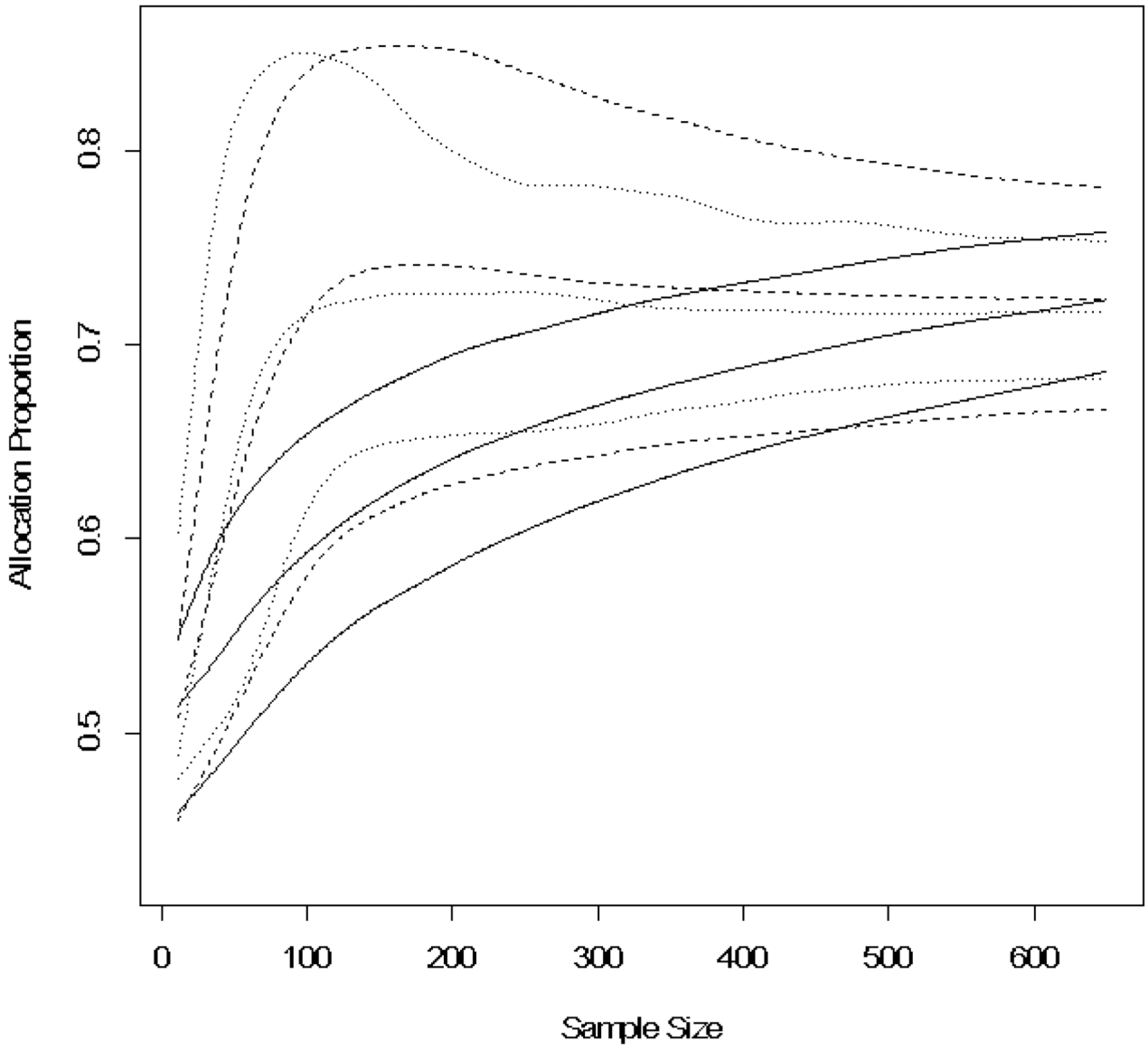

Fig. 4.

Allocation proportion and its 25th and 75th percentiles for the trial with $p_1 = 0.991$ and $p_2 = 0.941$ for third order urn design (solid lines), the doubly adaptive coin design with $\gamma = 2$ (dashed lines), and ERADE with $\pi = 0.5$ (dotted lines) plotted against the sample size.