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Optimal responses-adaptive designs based on efficiency, ethic, and cost

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The trade-off between power and ethical concerns has been well discussed by researchers. The total costs, however, has hardly ever been considered in the adaptive design of clinical trials. In this article, we derive the compromised optimal allocations based on costs, ethical concerns, and efficiency for clinical trials with binary and normal responses. The compromised optimal allocations are implemented with a doubly biased coin design (DBCD) based on Hu and Zhang's allocation function. The properties of the proposed designs are studied both theoretically and numerically. In many cases, the proposed designs are more efficient, economical and ethical than complete randomization (equal allocation) under both binary and normal responses.

Keywords and phrases: Asymptotical normality, Binary response, Clinical trial, Doubly adaptive biased coin design (DBCD), Normal response, Sequential method.

1. INTRODUCTION

Clinical trials are complex experiments on humans with multiple, often competing, objectives. The optimal allocation, which minimizes the exposure to effectiveness inferior treatments and maximizes power at the same time, has been extensively discussed theoretically and numerically in literature. However, when designing a clinical trial, people also have to take the monetary concerns into account. In fact, there are so many sources of costs in clinical trails, for example, patient recruitment costs, physician costs, clinical procedure costs, central Lab costs, and medicine costs. Medicine costs is one of the most important costs in clinical trails, because for a single disease, the costs of different treatments varies. Take the HIV disease for instance, the medicine named Enfuvirtide (Fuzeon) could cost \$4097.78 per month on average, while the medicine named Abacavir (Ziagen) would cost only \$670.37 per month on average. In addition, the medicine may be priced differently based on location. For some impoverished area in Africa, a common HIV medicine may become unaffordable because of the scarce resource. Therefore, treatment and medicine costs could have significant effect on clinical trials and cannot be overlooked. From both the patients' and decision maker's aspects, it is important to find optimal allocations to balance the monetary costs and ethical concerns for a fixed power.

Starting from the early of the 20th century, many new allocation methods have been proposed to enhance the design of multiobjective and multiarm clinical trials, including truncated binomial design, permuted block design, Efron's biased coin design (Efron, 1971) [4], Wei's urn design (Wei, 1977, 1978) [24], [25]), and generalized biased coin design (Smith, 1984, JRSSB). Instead of using a fixed allocation rule that assigning each patient to different treatments with equal probabilities, these designs incorporate the adaptive randomization for providing improvements over traditional balanced allocation designs both in terms of statistical efficiency and ethical criteria.

The preliminary idea of response-adaptive randomization (RAR) was derived by Thompson (1933) [21] and Robbins (1952) [14]. After them, Zelen put forth the play-the-winner (PW) rule (Zelen, 1969) [27], i.e., assigning the next patient to the same treatment if a success; assigning the next patient to the opposite treatment if a failure. Considering that the PW rule is not a randomized design, Wei and Durham proposed the randomized play-the-winner (RPW) rule in 1978 (Wei and Durham, 1978) [26].

Tracing back the history in response-adaptive randomization designs, we find two major families. One is the urn models family, its representatives include PW rule, RPW rule, generalized Friedman's urn models (Wei, 1978) [25]; (Smythe, 1996) [18]; (Bai, Hu and Shen, 2002) [2], randomized Polya urn (Durham, Flournoy, and Li, 1998) [3]), ternary urn (Ivanova and Flournoy, 2001 [11]), drop-the-loser rule (Ivanova, 2003) [12], generalized drop-the-loser rule (Zhang, Chan, Cheung and Hu, 2007) [28], etc. The other is the doubly adaptive biased coin designs family, represented by Eisele and Woodroofe (1995) [5], Hu and Zhang (2004) [9], Hu and Rosenberger (2003) [6], ERADE (Hu, Zhang and He, 2009) [10], etc.

One can find rich literatures on response-adaptive randomization procedures based on power and ethical concerns in clinical trials. Rosenberger et al. (2001) [17] proposed the optimal allocation aiming at minimizing the treatment failures and maximizing the power for two-arm binary response trials. Zhang et al. (2005) [29] studied the similar problem refers to power and ethics for continuous outcomes. Tymofyeyev et al. (2007) [22] mathematically set up the optimization problem concerning with both the number of treatment failures and power for a multi-arm clinical trial with dichoto-

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mous response, while Jeon et al. (2010) [13] gave the close form solution of the proposed optimization problem for a special case of three-treatment trials. However, none of them took the monetary cost into consideration.

In this article, we input the monetary costs into the optimization criteria for clinical trials, together with ethical concerns and efficiency. One significance of our work is that we balance the trade-off between costs and ethical concerns with a compromised parameter. The basic idea is to combine the objective of costs and ethical concerns using a tunning parameter as a weighted coefficient, which can be adjusted according to different preferences. The optimal allocation is then derived based on this combined objective. We will implement the derived optimal allocation by using response adaptive designs for two-treatment clinical trials with both binary and normal responses. The advantages of the proposed procedure are often: (1) improving the power; (2) reducing the total monetary costs; and (3) putting more patients to an overall "better" treatment arm.

The paper is organized as follows. In section 2, we state the general framework and deduce the compromised optimal allocation proportions for binary and normal responses trials. Doubly adaptive biased coin design (DBCD) is then used to implement the proposed optimal allocations. Theoretical properties of the proposed procedures are obtained. Section 3 compares our proposed procedure with the complete randomization for both binary and normal cases. We see by simulation that our proposed method increases average therapeutic effects and decreases the total cost over equal allocation without significant loss in power. We draw conclusions in Section 4. The main proofs are presented in the appendix.

2. OPTIMAL ALLOCATION AND IMPLEMENTATION

Assume n_1 and n_2 patients will be assigned to treatment 1 and 2, respectively, and $n_1 + n_2 = n$. Tymofyeyev *et al.* (2007) [22] formulated a general framework of the optimal allocation proportion:

$$\begin{aligned} &\min_{n_1,n_2} \sum_{j=1}^{2} w_j n_j, \\ &\text{such that } \; n_k \geq 0,\; k = 1,2 \\ &\qquad\qquad \phi(n_1, n_2) = K, \end{aligned} \tag{1}$$

where $\phi(n_1, n_2)$ is a constraint function, K is a positive constant, and $\mathbf{w} = (w_1, w_2)'$ is a vector with positive components. Note that problem (1) is usually a convex optimization problem. Now we fit our consideration under this framework for binary and normal responses.

2.1 Binary responses

For binary responses, the success (failure) probabilities of these two treatments are $p_1(q_1)$, and $p_2(q_2)$ respectively. The monetary cost of each patient in treatment 1 (and 2) is c_1 (and c_2). For testing $p_1 = p_2$, the constraint function $\phi(n_1, n_2)$ in the general framework above is the asymptotic variance of the test statistics, which can be written as:

$$\phi(n_1, n_2) = \frac{p_1 q_1}{n_1} + \frac{p_2 q_2}{n_2}. \tag{2}$$

To choose the coefficients w_1, w_2, we have to consider both ethic and cost here. We use $\mathbf{w} = (w_1, w_2)' = (\lambda q_1 + (1-\lambda)c_1, \lambda q_2 + (1-\lambda)c_2)'$, where $\lambda \in [0,1]$ is a weighted coefficient called the compromised parameter. The objective function $\min_{n_1,n_2} \sum_{j=1}^{2} w_j n_j$ in (1) turns into a weighted sum of costs and treatment failures with weights λ and $1-\lambda$. When $\lambda = 0$, we have $w_i = c_i$ $(i = 1, 2)$, and costs become the only concern in this optimal problem. If $\lambda = 1$, we only consider the ethical concern, and $w_i = q_i$ $(i = 1, 2)$. λ can be adjusted according to different preferences. If a disease is a matter of life and death, but the prices of different medicines are similar, then $\lambda > 0.5$ can be chosen to concentrate more on the ethical concerns. For example, the breast cancer. While, if a disease is not life-threatening, or the prices of two treatments have a huge difference, then $\lambda < 0.5$ could be selected to emphasize more on reducing total costs, for instance, the HIV example we mentioned in the introduction. When the ethical and costs concerns equally matter, it is reasonable to choose λ around 0.5. The optimal allocation proportion is stated in the following theorem.

Theorem 2.1. *When ϕ is defined in (2), and $w_i = \lambda q_i + (1-\lambda)c_i,\;\; i = 1, 2$, then the optimal allocation proportions $\rho^* = (\rho_1^*, \rho_2^*)'$ is given as follows:*

$$\begin{aligned} \rho_1^* &= \frac{\sqrt{w_2 p_1 q_1}}{\sqrt{w_1 p_2 q_2} + \sqrt{w_2 p_1 q_1}}, \;\; \textit{and} \\ \rho_2^* &= 1 - \rho_1^* = \frac{\sqrt{w_1 p_2 q_2}}{\sqrt{w_1 p_2 q_2} + \sqrt{w_2 p_1 q_1}}. \end{aligned} \tag{3}$$

In this paper, we call $R^* = n_1/n_2$ the compromised optimal allocation, with the following expression:

$$R^* = \left(\frac{w_2 p_1 q_1}{w_1 p_2 q_2}\right)^{\frac{1}{2}}, \tag{4}$$

where the compromised parameter λ reflects the trade-off between cost and ethical concern. Note that if $\lambda = 1$, then $R^* = n_1/n_2 = (p_1/p_2)^{1/2}$, which is the same as the result given by Rosenberger *et al.* (2001) [17]. If $\lambda = 0$, then $R^* = [c_2 p_1 q_1/(c_1 p_2 q_2)]^{1/2}$, which minimizes the total cost only.

2.2 Normal responses

Assume the responses of treatment 1 and 2 are from the normal distributions $N(\mu_1, \sigma_1^2)$ and $N(\mu_2, \sigma_2^2)$, respectively. μ_1 and μ_2 are the means and σ_1^2, σ_2^2 are the corresponding variances. Here we suppose a smaller response is better in ethical concern. c_1 and c_2 are the costs of each patient under two treatments respectively.

For testing $\mu_1 = \mu_2$, the constraint function $\phi(n_1, n_2)$ is

$$\phi(n_1, n_2) = \frac{\sigma_1^2}{n_1} + \frac{\sigma_2^2}{n_2}, \tag{5}$$

which is the asymptotic variance of the test statistics. Let $\mathbf{w} = (w_1, w_2)' = (\lambda\mu_1 + (1-\lambda)c_1, \lambda\mu_2 + (1-\lambda)c_2)'$, where $\lambda \in [0, 1]$ is again the weighted coefficient. Then the objective function in (1) becomes a weighted sum of costs and treatment responses with weights λ and $1-\lambda$. We have the following theorem.

Theorem 2.2. *Under the objective function $\phi(n_1, n_2)$ defined in (5), when $\mathbf{w} = (w_1, w_2)' = (\lambda\mu_1 + (1-\lambda)c_1, \lambda\mu_2 + (1-\lambda)c_2)'$, $k = 1, 2$, the optimal allocation proportions are given by $\rho^* = (\rho_1^*, \rho_2^*)'$, with components*

$$(6)\quad \rho_1^* = \frac{\sqrt{w_2\sigma_1^2}}{\sqrt{w_1\sigma_2^2} + \sqrt{w_2\sigma_1^2}}, \text{ and } \rho_2^* = \frac{\sqrt{w_1\sigma_2^2}}{\sqrt{w_1\sigma_2^2} + \sqrt{w_2\sigma_1^2}}.$$

The optimal allocation proportion for normal responses is $R^* = [w_2\sigma_1^2/(w_1\sigma_2^2)]^{1/2}$. Note that if $\lambda = 0$, we have $R^* = \sigma_1\sqrt{c_2}/(\sigma_2\sqrt{c_1})$, which minimizes the cost only. While if $\lambda = 1$, we get the allocation ratio minimizes the mean responses, and $R^* = \sigma_1\sqrt{\mu_2}/(\sigma_2\sqrt{\mu_1})$, which is the optimal allocation discussed by Zhang and Rosenberger (2005) [29].

Note that Theorem 2.1 and 2.2 are both derived from the convex optimization problem (1), and the details are provided in the Appendix.

2.3 Implementation with DBCD

Doubly adaptive biased coin design (DBCD) is an important family of response-adaptive randomization procedures for clinical trials. It uses sequentially updated estimation to skew the allocation probability to favor the treatment that has performed better thus far. In 2004, Hu and Zhang proposed a new family of doubly adaptive biased coin designs for two treatments to realize the target allocation proportions, which is simple to implement and easy to understand for the practitioner. We use the allocation probability function of Hu and Zhang (2004) [9] to realize our proposed compromised optimal allocation, so we call this Hu and Zhang's procedure in this paper. The details of how to implement our proposed allocation proportions using Hu and Zhang's procedure is implemented as following:

(i) First assign m_0 patients to each treatment by restricted randomization procedure; (ii) Denote $N_k(m)$ the random patients number on treatment k after $m \geq 2m_0$ patients have received the treatments, here $k = 1, 2$. Then we assign the $(m+1)$st patient to treatment k with probability,

$$(7)\qquad g\big(N_k(m)/m, \widehat{\rho}_k^*(m)\big) = \frac{\widehat{\rho}_k^*(m)\big(\frac{\widehat{\rho}_k^*(m)}{N_k(m)/(m)}\big)^\gamma}{\sum_{i=1}^K \widehat{\rho}_i^*(m)\big(\frac{\widehat{\rho}_i^*(m)}{N_i(m)/(m)}\big)^\gamma},$$

where $\widehat{\rho}_k^*(m)$ is the estimated target allocation proportion for treatment k, $(k = 1, 2)$, based on previous m patients' responses. The degree of variability and randomization can be controlled by tuning a particular parameter $\gamma \in [0, \infty)$. In this article, we use $\gamma = 2$ as recommended by Hu and Rosenberger (2006) [8].

Based on the results in Hu and Zhang (2004) [9], we compute the asymptotic variances for both normal and binary responses. The details are in Appendix, and the results are stated in the following lemmas:

Lemma 1. *For the binary case, we have*

$$\frac{N_1(n)}{n} - \rho_1^* = O\left(\sqrt{\frac{\log\log n}{n}}\right) \text{ a.s.}$$
$$\text{and}\quad n^{1/2}\left(\frac{N_1(n)}{n} - \rho_1^*\right) \xrightarrow{\mathfrak{D}} N(0, \sigma_b^2),$$

where

$$\sigma_b^2 = \frac{(1+\gamma)\lambda^2 p_1q_1p_2q_2\Big(p_2q_2\psi\varphi^{-1/2} + p_1q_1\varphi\psi^{-1/2}\Big)}{2(1+2\gamma)\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}} + \frac{2(1+\gamma)\lambda\varphi\psi\Big(p_2q_2(q_1-p_1)\varphi^{-1/2} + p_1q_1(q_2-p_2)\psi^{-1/2}\Big)}{2(1+2\gamma)\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}} + \frac{\big(2+(1+\gamma)p_1q_1\big)\psi\varphi^{3/2} + \big(2+(1+\gamma)p_2q_2\big)\varphi\psi^{3/2}}{2(1+2\gamma)\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}},$$

$\varphi = w_1p_2q_2$, *and* $\psi = w_2p_1q_1$.

Lemma 2. *For the normal responses, we have*

$$\frac{N_1(n)}{n} - \rho_1^* = O\left(\sqrt{\frac{\log\log n}{n}}\right) \text{ a.s.}$$
$$\text{and}\quad n^{1/2}\left(\frac{N_1(n)}{n} - \rho_1^*\right) \xrightarrow{\mathfrak{D}} N(0, \sigma_n^2),$$

where

$$\sigma_n^2 = \frac{\sqrt{\eta}\zeta\big(2+(1+\gamma)(\nu+2)\big) + \sqrt{\zeta}\eta\big(2+(1+\gamma)(\delta+2)\big)}{2(1+2\gamma)\big(\sqrt{\zeta}+\sqrt{\eta}\big)^3},$$

$\zeta = w_1\sigma_2^2$, $\eta = w_2\sigma_1^2$, $\nu = \lambda^2 w_1^{-2}\sigma_1^2$, *and* $\delta = \lambda^2 w_2^{-2}\sigma_2^2$.

3. NUMERICAL STUDY

Now we consider numerical studies based on two-side tests. For binary trials, a two-sided hypothesis test is:

$$H_0 : \Delta = p_1 - p_2 = 0 \quad \text{versus} \quad H_1 : p_1 \neq p_2.$$

Similarly, for normal trials, a two-sided hypothesis test is given by:

$$H_0 : \Delta = \mu_1 - \mu_2 = 0 \quad \text{versus} \quad H_1 : \mu_1 \neq \mu_2.$$

In both cases, we use the Wald test (with a given significance level $\alpha = 0.05$). Considering the binary trials, the Wald test statistics is:

$$(8)\qquad Z = \frac{\widehat{p}_1 - \widehat{p}_2}{\sqrt{\widehat{p}_1\widehat{q}_1/n_1 + \widehat{p}_2\widehat{q}_2/n_2}},$$

where $\hat{p}_i$ $(i = 1, 2)$ are the simple means of the samples and $\hat{q}_i = 1 - \hat{p}_i$ $(i = 1, 2)$. This test tends to have inflated size.

Table 1. The Estimated sample size n and the Corresponding Simulated Power (parentheses) for the Compromised Optimal Allocations and Equal Allocation for Binary Responses

				Compromised Optimal Allocation					
p_1	p_2	c_1	c_2	$\lambda=0$	$\lambda=0.3$	$\lambda=0.5$	$\lambda=0.7$	$\lambda=1$	Equal Allocation
0.1	0.2	0.1	0.2	531(0.90)	516(0.91)	516(0.90)	516(0.89)	516(0.89)	526(0.88)
0.1	0.2	0.2	0.1	531(0.89)	518(0.89)	517(0.90)	516(0.90)	516(0.89)	526(0.89)
0.1	0.2	0.1	0.4	578(0.89)	521(0.91)	516(0.89)	515(0.88)	515(0.90)	526(0.92)
0.1	0.2	0.4	0.1	578(0.89)	526(0.89)	520(0.91)	517(0.90)	516(0.90)	526(0.89)
0.4	0.6	0.1	0.2	260(0.90)	253(0.90)	253(0.90)	254(0.89)	255(0.90)	254(0.90)
0.4	0.6	0.2	0.1	260(0.89)	257(0.90)	256(0.91)	256(0.89)	255(0.89)	254(0.90)
0.4	0.6	0.1	0.4	284(0.89)	256(0.90)	253(0.89)	253(0.90)	255(0.89)	254(0.90)
0.4	0.6	0.4	0.1	284(0.89)	265(0.90)	260(0.89)	257(0.90)	255(0.89)	254(0.90)
0.7	0.9	0.1	0.2	156(0.90)	152(0.89)	152(0.91)	155(0.90)	162(0.90)	162(0.89)
0.7	0.9	0.2	0.1	156(0.91)	158(0.90)	159(0.91)	160(0.92)	162(0.92)	162(0.89)
0.7	0.9	0.1	0.4	169(0.87)	155(0.86)	152(0.88)	152(0.90)	162(0.91)	162(0.90)
0.7	0.9	0.4	0.1	169(0.92)	167(0.91)	166(0.91)	165(0.91)	162(0.89)	162(0.90)

Table 2. Simulation Results for the Compromised Optimal Allocation with Different λ Values and Equal Allocation for Binary Responses(1000 Replications)

					Compromised Optimal Allocation					
p_1	p_2	c_1	c_2	n	$\lambda=0$	$\lambda=0.3$	$\lambda=0.5$	$\lambda=0.7$	$\lambda=1$	Equal Allocation
					Simulated Means of the Allocation Proportion n_1/n					
0.1	0.2	0.4	0.6	526	0.48	0.45	0.44	0.42	0.41	0.50
0.1	0.2	0.6	0.4	526	0.38	0.39	0.40	0.41	0.41	0.50
					The Powers					
0.1	0.2	0.4	0.6	526	0.92	0.90	0.90	0.89	0.89	0.90
0.1	0.2	0.6	0.4	526	0.91	0.89	0.89	0.90	0.90	0.90
					Simulated Expected Failures					
0.1	0.2	0.4	0.6	526	445.66	444.42	443.71	443.46	442.59	447.22
0.1	0.2	0.6	0.4	526	441.06	441.24	442.01	442.20	442.63	447.21
					Simulated Expected Total Costs					
0.1	0.2	0.4	0.6	526	265.20	268.44	269.80	270.91	272.15	263.09
0.1	0.2	0.6	0.4	526	250.01	251.75	252.55	253.11	253.87	262.98

In order to avoid this error, we have utilized an adjustment by Agresti and Caffo (2000) [1]. Replace $\widehat{p}_1$ and $\widehat{p}_2$ by:

$$\widehat{p}_1* = \frac{s_1+0.5}{n_1+1} \text{ and } \widehat{p}_2* = \frac{s_2+0.5}{n_2+1} \tag{9}$$

respectively, where s_1 and s_2 are observed success on treatment 1 and 2.

For normal responses trials, however, the Wald test statistics is given by:

$$Z = \frac{\widehat{\mu}_1 - \widehat{\mu}_2}{\sqrt{\widehat{\sigma}_1^2/n_1 + \widehat{\sigma}_2^2/n_2}}, \tag{10}$$

where $\widehat{\mu}_i$ and $\widehat{\sigma}_i$ are the usual unbiased estimators $(i=1,2)$.

The requisite sample size n that yields power of β for a binary responses trial with the allocation proportion n_1/n_2 equaling to R can be calculated as follows:

$$n = \frac{(z_{(\alpha/2)} - z_{(\beta)})^2\big((1+R)p_1q_1/R + (1+R)p_2q_2\big)}{(p_1-p_2)^2}, \tag{11}$$

where $z_{(\beta)}$ is the upper quantile of standard normal distribution. The sample size of our compromised optimal allocation (4) is then:

$$n = \frac{(z_{(\alpha/2)} - z_{(\beta)})^2\big((w_1+w_2)p_1q_1p_2q_2 + (p_1q_1+p_2q_2)\sqrt{\kappa\omega}\big)}{\sqrt{\kappa\omega}(p_1-p_2)^2}, \tag{12}$$

where $\kappa = w_1p_1q_1$, and $\omega = w_2p_2q_2$.

For a normal two-arm trial, with the allocation proportion n_1/n_2 equaling to R, the requisite sample size n to achieve power β is:

$$(13)\qquad n = \frac{(z_{(\alpha/2)} - z_{(\beta)})^2\big((1+R)\sigma_1^2/R + (1+R)\sigma_2^2\big)}{(\mu_1-\mu_2)^2}.$$

The sample size for compromised optimal allocation is:
(14)

$$n = \frac{(z_{(\alpha/2)} - z_{(\beta)})^2\big((w_1+w_2)\sigma_1^2\sigma_2^2 + (\sigma_1^2+\sigma_2^2)\sqrt{w_1\sigma_1^2 w_2\sigma_2^2}\big)}{\sqrt{w_1\sigma_1^2 w_2\sigma_2^2}(\mu_1-\mu_2)^2}.$$

3.1 Binary responses

In all numerical studies, we randomly assign 5 patients to both treatments by restricted randomization (Hu and Rosenberger (2006) [8]), then we switch to our proposed procedures. Each simulation is based on 1000 replications.

We first calculate the requisite sample sizes that yield power of 0.90 for compromised optimal allocations and equal allocation, then we obtain the simulated power based on 1000 simulated trials. The results is reported in Table 1. In most cases, the requisite sample sizes of our proposed procedures are smaller than or similar to that for equal allocation. However, there are cases where the sample sizes are larger than equal allocation, for example, when $\lambda = 0$ and the costs $c_1 = 0.1$, $c_2 = 0.4$ for binary responses. In fact, we find that when $\lambda = 0$ and the costs c_1, c_2 are large, the requisite sample sizes of our proposed procedures tend to be large, because the experimental objective is to minimize costs only when $\lambda = 0$, while equal allocation will neglect the costs effect on its sample size, especially when the costs are high. Therefore, our proposed procedure with $\lambda = 0$ may require large sample size to incorporate costs effects when the costs are high. More details and discussions on sample size formulas for randomization procedures can be found in chapter 6 of the book by Hu and Rosenberger [7].

In the following numerical studies, we use sample size n that yields 0.90 power for the test of homogeneity based on equal allocation. We report the following four measures: 1) The allocation proportions; 2) The power; 3) The expected number of treatment failures (The average value of responses); and 4) The total cost. In our simulations, we use the same values of p_1, p_2 from Rosenberger et al. (2001) [17]. Without loss of generality, we choose c_1 and c_2 between 0 and 1 here. The results are in Table 2.

According to Table 2, we find that our procedures work well especially when p_1 and p_2 are small to moderate. We see that the compromised parameter λ plays an important role in balancing the trade-off between ethics and total costs. In most cases, our proposed procedures with different λ values do not have significant loss in power compared with the equal allocation. However, when $p_1 = 0.1$, $p_2 = 0.2$, $c_1 = 0.4$, and $c_2 = 0.6$, compromised optimal adaptive allocations with λ less than one lead to 2-9 more monetary costs than the equal allocation, but they reduce 2-5 treatment failures as a compensation. To figure out the reason why it costs more than equal allocation when $\lambda = 0$ for the case $p_1 = 0.1$, $p_2 = 0.2$, $c_1 = 0.4$, $c_2 = 0.6$, and $n = 526$, we theoretically calculate the expected costs based on the optimal allocation proportions in (3):

$$\begin{aligned}\rho_1^* &= \frac{\sqrt{w_2p_1q_1}}{\sqrt{w_1p_2q_2}+\sqrt{w_2p_1q_1}}\\ &= \frac{\sqrt{0.6\times 0.1\times 0.9}}{\sqrt{0.4\times 0.2\times 0.8}+\sqrt{0.6\times 0.1\times 0.9}}\\ &= 0.4788,\end{aligned}$$

therefore the expected cost using the optimal allocation is:

$$\text{Cost(optimal)} = \rho_1^*\times n\times c_1 + (1-\rho_1^*)\times n\times c_2 = 265.2328,$$

while for equal allocation, the expected cost is

$$\text{Cost(equal)} = 0.5\times n\times c_1 + 0.5\times n\times c_2 = 263.$$

The theoretical results match with the simulation results (265.20 for optimal allocation and 263.09 for equal allocation) in Table 2. Although the optimal allocation is aimed at minimizing the cost when $\lambda = 0$ ($w_1 = c_1$ and $w_2 = c_2$), the allocation formula derived in (3) not only depends on costs but also depends on p_1 and p_2 in that the total costs is minimized on condition that $\phi(n_1, n_2) = (p_1q_1)/n_1 + (p_2q_2)/n_2$ is fixed at a constant level K, i.e., the efficiency to test $p_1 = p_2$ must be first guaranteed to minimize the cost. Besides, if p_1 and p_2, c_1 and c_2 are very close to each other, the allocation proportions will be close to 0.5, and it is also likely that the allocation proportions are dominated by p_1 and p_2, like in our case, when $p_1 = 0.1$, $p_2 = 0.2$, $c_1 = 0.4$, $c_2 = 0.6$, we have $\rho_1^* = 0.4788 < 0.50$. More than half of the patients are assigned to treatment 2, the more expensive treatment. But to look at a positive side, even though the costs is about 2.11 higher than equal allocation, our method can reduce 2 treatment failures as a compensation. We also implement several different combinations of parameters, similar results are obtained.

3.2 Normal responses

In the following simulations, we choose the same values of μ_1, μ_2, σ_1, and σ_2 from Hu and Rosenberger (2006) [8]. c_1 and c_2 are restricted to be between 5 to 20 to match the mean values. The requisite sample sizes are listed in Table 3. Our proposed procedure performs better with regard to requisite sample size and often reduces 2-5 patients from equal allocation in average in Table 3.

In Table 4, we report the simulated means of n_1/n and the theoretical proportions, the powers, the expected values of overall responses, and the expected values of total costs, respectively. First the simulated proportions of our proposed procedure match their corresponding theoretical ones. The proposed procedure performs pretty well in terms of power. It can be seen that for all sets of parameters, our procedure is more powerful than complete randomization in Table 4.

We also find that when $\mu_1 < \mu_2$, $\sigma_1 > \sigma_2$, and $c_1 < c_2$, the proposed procedure works well in reducing both the

Table 3. The Estimated sample size n and the Corresponding Simulated Power(parentheses) for the Compromised Optimal Allocations and Equal Allocation(Equal) for Normal Responses

						Compromised Optimal Allocation					
μ_1	μ_2	σ_1	σ_2	c_1	c_2	$\lambda = 0$	$\lambda = 0.3$	$\lambda = 0.5$	$\lambda = 0.7$	$\lambda = 1$	Equal
13	15	4	2.5	10	20	115(0.91)	113(0.90)	113(0.92)	112(0.91)	112(0.89)	117(0.89)
13	15	4	2.5	20	10	115(0.89)	113(0.90)	112(0.90)	112(0.91)	112(0.92)	117(0.91)
13	15	2.5	4	10	20	115(0.91)	113(0.91)	113(0.89)	112(0.92)	112(0.90)	117(0.89)
13	15	2.5	4	20	10	115(0.90)	113(0.90)	112(0.91)	112(0.90)	112(0.93)	117(0.89)
13	15	4	2.5	7	9	112(0.90)	112(0.91)	112(0.90)	112(0.90)	112(0.91)	117(0.90)
13	15	4	2.5	9	7	112(0.91)	112(0.90)	112(0.92)	112(0.92)	112(0.91)	117(0.88)
13	15	2.5	4	7	9	112(0.91)	112(0.92)	112(0.91)	112(0.91)	112(0.91)	117(0.89)
13	15	2.5	4	9	7	112(0.91)	112(0.90)	112(0.91)	112(0.91)	112(0.91)	117(0.89)

Table 4. Simulation Results for the Compromised Optimal Allocation with Different λ Values and Equal Allocation for Normal Responses (1000 Replications)

							Compromised Optimal Allocation					
μ_1	μ_2	σ_1	σ_2	c_1	c_2	n	$\lambda = 0$	$\lambda = 0.3$	$\lambda = 0.5$	$\lambda = 0.7$	$\lambda = 1$	Equal
Simulated Means of the Proportion n_1/n and Theoretical Allocation Proportions(parentheses)												
13	15	4	2.5	10	20	117	.70(.69)	.68(.68)	.67(.66)	.65(.65)	.64(.63)	.50
13	15	4	2.5	20	10	117	.53(.53)	.56(.56)	.59(.58)	.61(.60)	.64(.63)	.50
13	15	2.5	4	10	20	117	.47(.47)	.45(.45)	.43(.44)	.42(.42)	.40(.40)	.50
13	15	2.5	4	20	10	117	.30(.31)	.33(.33)	.35(.35)	.37(.37)	.40(.40)	.50
The Powers												
13	15	4	2.5	10	20	117	0.92	0.91	0.92	0.91	0.92	0.89
13	15	4	2.5	20	10	117	0.91	0.92	0.93	0.93	0.91	0.91
13	15	2.5	4	10	20	117	0.91	0.92	0.92	0.92	0.91	0.89
13	15	2.5	4	20	10	117	0.91	0.91	0.92	0.92	0.92	0.89
Simulated Expected Value of Overall Responses												
13	15	4	2.5	10	20	117	13.60	13.63	13.68	13.69	13.73	13.99
13	15	4	2.5	20	10	117	13.92	13.87	13.84	13.78	13.73	14.01
13	15	2.5	4	10	20	117	14.06	14.11	14.14	14.15	14.20	13.99
13	15	2.5	4	20	10	117	14.40	14.35	14.31	14.26	14.22	14.01
Simulated Expected Total Costs												
13	15	4	2.5	10	20	117	1522.29	1542.65	1560.28	1574.18	1594.04	1752.87
13	15	4	2.5	20	10	117	1794.09	1828.19	1855.03	1880.15	1915.43	1752.23
13	15	2.5	4	10	20	117	1790.19	1816.73	1833.72	1847.18	1871.25	1753.17
13	15	2.5	4	20	10	117	1520.46	1552.84	1578.90	1602.66	1632.76	1753.74

expected values of overall responses and the expected values of total monetary costs from equal allocation rule. If $\mu_1 < \mu_2$, $\sigma_1 > \sigma_2$, and $c_1 > c_2$, the proposed procedure increases the total costs but decrease the average responses from equal allocation as a compensation. When $\lambda = 0$, the procedure tends to assign more patients to the treatment with low cost. When c_2/c_1 is smaller than μ_2/μ_1, for example, when $\mu_1 = 13$, $\mu_2 = 15$, $c_1 = 20$, and $c_2 = 10$, the procedure with $\lambda = 1$ would yield the smaller average response, which agrees with the theoretical results. The compromised parameter λ does play an important role in the trade-off between ethics and total costs.

4. CONCLUSION REMARKS

In this paper, we consider cost as an additional objective together with ethical concerns and efficiency in clinical trials. By combining the cost with ethical concerns to a weighted objective, we obtain the compromised optimal allocation. Then the DBCD (Hu and Zhang, 2004) [9] is used to implement the proposed compromised optimal allocation. Both theoretical and numerical results support the proposed procedure.

For the binary responses, the compromised adaptive rule is particularly useful when success probabilities of the treatments p_1 and p_2 are small to moderate, and the distinction between c_1 and c_2 is not striking. The compromised optimal allocation (4) is a generalization form of the optimal allocation given by Rosenberger et al. (2001) [17]. For the normal responses, under the same setting as the book of Hu and Rosenberger (2006) [8], the compromised adaptive design is often more effective and economical by comparing with equal allocation rule. The compromised parameter λ plays an important role in balancing the trade-off between the treatment effects and total costs, and provides our compromised optimal allocation with the flexibility to adjust to different objectives.

In numerical studies, we have little knowledge of the two treatments at the beginning, and 5 patients are assigned to each of the two treatments by using restricted randomization procedure. Starting from the 11 patient, we switch to our proposed procedures. The details of restricted randomization procedure can be found in chapter 1 of the book by Hu and Rosenberger [7], which is beyond the scope of this paper.

We only consider about comparing two treatments in this paper. It is worth to point out that the framework can be generalized to three or more treatments as Tymofyeyev *et al.* (2007) [22] (for binary responses) and Zhu and Hu (2009) [30] (for continuous responses). The corresponding analytical solutions could be difficult to obtain, and the expression could be too complicated as indicated in Jeon and Hu (2010) [13] and Zhu and Hu (2009) [30] for the special case ($\lambda = 1$). However, one can always implement the proposed procedure numerically.

APPENDIX A. TECHNICAL PROOFS

A.1 Proofs of Theorems 2.1 and 2.2

Proof. For binary responses, the optimal allocation proportion $R^* = n_1/n_2$ can be expressed as:

(15)

$$R^* = \arg\min_R \{w_1 n_1 + w_2 n_2\} = \arg\min_R \{\frac{n(Rw_1 + w_2)}{R+1}\}$$

and $n = n(R, p_1, p_2)$ is obtained by solving the equation $\text{var}(\widehat{p}_1 - \widehat{p}_2) = K$, which yields:

$$n = \frac{(1+R)(p_1q_1 + Rp_2q_2)}{KR}. \tag{16}$$

Now substituting (16) into the criterion function in equation (15), taking the derivative with respect to R and equating it to zero, we can get

$$R^* = \left(\frac{w_2 p_1 q_1}{w_1 p_2 q_2}\right)^{\frac{1}{2}}.$$

Note that R^* does not depend on K, so we obtain:

$$\rho_1^* = \frac{R^*}{R^*+1} = \frac{\sqrt{w_2p_1q_1}}{\sqrt{w_1p_2q_2} + \sqrt{w_2p_1q_1}}$$

and

$$\rho_2^* = 1 - \rho_1^* = \frac{\sqrt{w_1p_2q_2}}{\sqrt{w_1p_2q_2} + \sqrt{w_2p_1q_1}}. \qquad \square$$

The proof of Theorem 2.2 is similar to Theorem 2.1. We omit the details here.

A.2 Proof of Lemma 1

Proof. For binary responses, we rewrite ρ_1^* given in Theorem 2.1 as

$$\rho(p_1, p_2) = \frac{\sqrt{w_2(p_1 - p_1^2)}}{\sqrt{w_1(p_2 - p_2^2)} + \sqrt{w_2(p_1 - p_1^2)}}.$$

Then

$$\begin{aligned}\nabla(\rho)|_{(p_1,p_2)} =& \Bigg(\frac{w_2(q_1 - p_1)\frac{\sqrt{w_1p_2q_2}}{\sqrt{w_2p_1q_1}} + \lambda p_2q_2\frac{\sqrt{w_2p_1q_1}}{\sqrt{w_1p_2q_2}}}{2\big(\sqrt{w_1p_2q_2} + \sqrt{w_2p_1q_1}\big)^2}, \\ & \frac{-w_1(q_2 - p_2)\frac{\sqrt{w_2p_1q_1}}{\sqrt{w_1p_2q_2}} - \lambda p_1q_1\frac{\sqrt{w_1p_2q_2}}{\sqrt{w_2p_1q_1}}}{2\big(\sqrt{w_2p_1q_1} + \sqrt{w_1p_2q_2}\big)^2}\Bigg),\end{aligned}$$

and according to Hu and Zhang (2004), $\tau_3^2 = (\nabla(\rho)|_{p_1,p_2})'\mathbf{V}(\nabla(\rho)|_{p_1,p_2})$, $\tau_1^2 = \rho_1^*(1-\rho_1^*)$, where $\mathbf{V} = \text{diag}\Big(p_1q_1/\rho_1^*, p_2q_2/(1-\rho_1^*)\Big)$. Therefore, τ_3^2 and τ_1^2 can be calculated as:

$$\begin{aligned}\tau_3^2 =& \frac{w_2(q_1-p_1)^2\varphi^{3/2} + w_1(q_2-p_2)^2\psi^{3/2}}{4\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}} + \\ & \frac{\lambda^2 p_1q_1p_2q_2\Big(p_2q_2\psi\varphi^{-1/2} + p_1q_1\varphi\psi^{-1/2}\Big)}{4\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}} + \\ & \frac{2\lambda\varphi\psi\Big(p_2q_2(q_1-p_1)\varphi^{-1/2} + p_1q_1(q_2-p_2)\psi^{-1/2}\Big)}{4\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}}\end{aligned}$$

and

$$\tau_1^2 = \frac{\sqrt{\psi\varphi}}{\big(\sqrt{\psi}+\sqrt{\varphi}\big)^2},$$

where

$$\varphi = w_1p_2q_2, \text{ and } \psi = w_2p_1q_1.$$

Therefore, by Hu and Zhang(2004),

$$\frac{N_1(n)}{n} - \rho_1^* = O\left(\sqrt{\frac{\log\log n}{n}}\right) \quad \text{a.s.} \quad \text{and}$$

$$n^{1/2}\left(\frac{N_1(n)}{n} - \rho_1^*\right) \xrightarrow{\mathfrak{D}} N(0, \sigma_b^2),$$

where

$$\sigma_b^2 = \frac{(1+\gamma)\lambda^2 p_1q_1p_2q_2\Big(p_2q_2\psi\varphi^{-1/2} + p_1q_1\varphi\psi^{-1/2}\Big)}{2(1+2\gamma)\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}} +$$

$$\frac{2(1+\gamma)\lambda\varphi\psi\Big(p_2q_2(q_1-p_1)\varphi^{-1/2}+p_1q_1(q_2-p_2)\psi^{-1/2}\Big)}{2(1+2\gamma)\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}}+$$
$$\frac{\big(2+(1+\gamma)p_1q_1\big)\psi\varphi^{3/2}+\big(2+(1+\gamma)p_2q_2\big)\varphi\psi^{3/2}}{2(1+2\gamma)\big(\sqrt{\psi}+\sqrt{\varphi}\big)^3\sqrt{\psi\varphi}},\qquad\square$$

A.3 Proof of Lemma 2

Proof. Suppose that $\{\{\xi_{m,k}, m=1,2,\ldots\}, k=1,2\}$ are the responses vectors in $\mathbb{R}^d$, where $\xi_{m,k}=(\xi_{m,k_1},\ldots,\xi_{m,k_d})$ is the response of the mth patient on treatment k, $k=1,2$. Let θ_1 and θ_2 be the corresponding parameters of treatment 1 and treatment 2, respectively. For simplicity of notation, we assume that both θ_1 and θ_2 are d-dimensional parameters, and $\theta_1=E\xi_{1,1}$ and $\theta_2=E\xi_{1,2}$. So we have $\theta_1=(\theta_{11},\ldots,\theta_{1d})=(E\xi_{1,11},\ldots,E\xi_{1,1d})$ and $\theta_2=(\theta_{21},\ldots,\theta_{2d})=(E\xi_{1,21},\ldots,E\xi_{1,2d})$.

For normal responses, $X_1,X_2,\cdots,X_{n_1}$ and $Y_1,Y_2,\cdots,Y_{n_2}$ are outcome indicators of treatment 1 receivers and treatment 2 receivers, respectively, which satisfy

$$X_1,X_2,\ldots\sim N(\mu_1,\sigma_1^2)\text{ and }Y_1,Y_2,\ldots\sim N(\mu_2,\sigma_2^2).$$

The desired proportion is given in Theorem 2.2, and

$$\rho_1^*=\frac{\sqrt{w_2\sigma_1^2}}{\sqrt{w_1\sigma_2^2}+\sqrt{w_2\sigma_1^2}}.$$

Set $\xi_{m,1}=(X_m^2,X_m)$ and $\xi_{m,2}=(Y_m^2,Y_m)$. Here, $\theta_{11}=EX_1^2$, $\theta_{12}=EX_1=\mu_1$, $\theta_{21}=EY_1^2$, $\theta_{22}=EY_1=\mu_2$. Then we rewrite ρ_1^* as a function of $\theta_{11},\theta_{12},\theta_{21}$, and θ_{22}, which is denoted by $\rho(\theta_{11},\theta_{12},\theta_{21},\theta_{22})$, and

$$\rho(\theta_{11},\theta_{12},\theta_{21},\theta_{22})=\frac{\sqrt{w_2(\theta_{11}-\theta_{12}^2)}}{\sqrt{w_1(\theta_{21}-\theta_{22}^2)}+\sqrt{w_2(\theta_{11}-\theta_{12}^2)}}.$$

Obviously, the function above is continuous in $\{\theta:\theta_{11}>\theta_{12}^2,\theta_{21}>\theta_{22}^2\}$ and is twice differentiable at $\Theta=(\theta_1,\theta_2)$. Therefore, we have:

$$\nabla(\rho)|_\Theta=\left(\frac{\partial\rho}{\partial\theta_{11}},\frac{\partial\rho}{\partial\theta_{12}},\frac{\partial\rho}{\partial\theta_{21}},\frac{\partial\rho}{\partial\theta_{22}}\right),$$

and

$$\begin{aligned}\nabla(\rho)|_\Theta=&\Bigg(\frac{w_1w_2\sigma_2^2}{2\big(\sqrt{w_1\sigma_2^2}+\sqrt{w_2\sigma_1^2}\big)^2\sqrt{w_2\sigma_1^2}\sqrt{w_1\sigma_2^2}},\\&\frac{w_1w_2\sigma_2^2(-2\mu_1-\lambda\sigma_1^2w_1^{-1})}{2\big(\sqrt{w_1\sigma_2^2}+\sqrt{w_2\sigma_1^2}\big)^2\sqrt{w_2\sigma_1^2}\sqrt{w_1\sigma_2^2}},\\&\frac{-w_1w_2\sigma_1^2}{2\big(\sqrt{w_1\sigma_2^2}+\sqrt{w_2\sigma_1^2}\big)^2\sqrt{w_2\sigma_1^2}\sqrt{w_1\sigma_2^2}},\\&\frac{w_1w_2\sigma_1^2(2\mu_2+\lambda\sigma_2^2w_2^{-1})}{2\big(\sqrt{w_1\sigma_2^2}+\sqrt{w_2\sigma_1^2}\big)^2\sqrt{w_2\sigma_1^2}\sqrt{w_1\sigma_2^2}}\Bigg).\end{aligned}$$

Note that

$$(1,-2\mu_1-\lambda\sigma_1^2w_1^{-1})\operatorname{Var}\{(X_1^2,X_1)\}(1,-2\mu_1-\lambda\sigma_1^2w_1^{-1})'=\operatorname{Var}\Big\{\Big(X_1-\big(\mu_1+\lambda\sigma_1^2(2w_1)^{-1}\big)\Big)^2\Big\},$$

and similarly,

$$(1,-2\mu_2-\lambda\sigma_2^2w_2^{-1})\operatorname{Var}\{(Y_1^2,Y_1)\}(1,-2\mu_2-\lambda\sigma_2^2w_2^{-1})'=\operatorname{Var}\Big\{\Big(Y_1-\big(\mu_2+\lambda\sigma_2^2(2w_2)^{-1}\big)\Big)^2\Big\}.$$

Now we get the expression of $\operatorname{Var}\Big\{\Big(X_1-\big(\mu_1+\lambda\sigma_1^2(2w_1)^{-1}\big)\Big)^2\Big\}$ as follows: Denote $Q=X_1-\mu_1$ and $Z=X_1-\big(\mu_1+\lambda\sigma_1^2(2w_1)^{-1}\big)=(X_1-\mu_1)-\lambda\sigma_1^2(2w_1)^{-1}=Q-\lambda\sigma_1^2(2w_1)^{-1}$. Since $Q/\sigma_1\sim N(0,1)$, we know that $EQ=0$, $E(Q^2)=\sigma^2$, $E(Q^3)=0$, and $E(Q^4)=3\sigma^4$. So it can be deduced that

$$\begin{aligned}E(Z^2)&=E\big(Q^2-\lambda\sigma_1^2(w_1)^{-1}Q+\lambda^2\sigma_1^4(2w_1)^{-2}\big)\\&=\sigma^2+\lambda^2\sigma_1^4(2w_1)^{-2},\end{aligned}$$

and

$$\begin{aligned}E(Z^4)=&E\big(Q^4-2\lambda\sigma_1^2w_1^{-1}Q^3+3\lambda^2\sigma_1^4(2w_1^2)^{-1}Q^2-\\&\lambda^3\sigma_1^6(2w_1^3)^{-1}Q+\lambda^4\sigma_1^8(16w_1^4)^{-1}\big)\\=&3\sigma_1^4+3\lambda^2\sigma_1^6(2w_1^2)^{-1}+\lambda^4\sigma_1^8(16w_1^4)^{-1},\end{aligned}$$

so $\operatorname{Var}\Big\{\Big(X_1-\big(\mu_1+\lambda\sigma_1^2(2w_1)^{-1}\big)\Big)^2\Big\}=\operatorname{Var}(Z^2)=E(Z^4)-\big(E(Z^2)\big)^2=\lambda^2\sigma_1^6w_1^{-2}+2\sigma_1^4$, and similarly, $\operatorname{Var}\Big\{\Big(X_2-\big(\mu_2+\lambda\sigma_2^2(2w_2)^{-1}\big)\Big)^2\Big\}=\lambda^2\sigma_2^6w_2^{-2}+2\sigma_2^4$.

According to the conditions on the allocation function and asymptotic results given by Hu and Zhang(2004), let

$$\tau_3^2=(\nabla(\rho)|_\Theta)'\mathbf{V}(\nabla(\rho)|_\Theta)\text{ and }\tau_1^2=\rho_1^*(1-\rho_1^*)$$

where $\mathbf{V}=\operatorname{diag}\Big(\frac{\operatorname{Var}(\xi_{1,1})}{\rho_1^*},\frac{\operatorname{Var}(\xi_{1,2})}{1-\rho_1^*}\Big)$. We have

$$\begin{aligned}\tau_3^2=&\frac{w_1^2w_2^2\sigma_2^2\big(\lambda^2\sigma_1^6w_1^{-2}+2\sigma_1^4\big)}{4\big(\sqrt{\zeta}+\sqrt{\eta}\big)^4\zeta\eta}\cdot\frac{\sqrt{\zeta}+\sqrt{\eta}}{\sqrt{\eta}}+\\&\frac{w_1^2w_2^2\sigma_1^2\big(\lambda^2\sigma_2^6w_2^{-2}+2\sigma_2^4\big)}{4\big(\sqrt{\zeta}+\sqrt{\eta}\big)^4\zeta\eta}\cdot\frac{\sqrt{\zeta}+\sqrt{\eta}}{\sqrt{\zeta}}\\=&\frac{\sqrt{\zeta\eta}\Big(\sqrt{\zeta}(\nu+2)+\sqrt{\eta}(\delta+2)\Big)}{4\big(\sqrt{\zeta}+\sqrt{\eta}\big)^3}\end{aligned}$$

and

$$\tau_1^2=\frac{\sqrt{\zeta\eta}}{\big(\sqrt{\zeta}+\sqrt{\eta}\big)^2},$$

where

$$\zeta = w_1\sigma_2^2,\ \eta = w_2\sigma_1^2,\ \nu = \lambda^2 w_1^{-2}\sigma_1^2,\ \text{and } \delta = \lambda^2 w_2^{-2}\sigma_2^2.$$

We know from Hu and Zhang(2004) that

$$\frac{N_1(n)}{n} - \rho_1^* = O\left(\sqrt{\frac{\log\log n}{n}}\right) \quad \text{a.s.} \quad \text{and}$$
$$n^{1/2}\left(\frac{N_1(n)}{n} - \rho_1^*\right) \xrightarrow{\mathfrak{D}} N(0, \sigma_n^2),$$

where

$$\sigma_n^2 = \frac{\sqrt{\eta}\zeta\big(2 + (1+\gamma)(\nu+2)\big) + \sqrt{\zeta}\eta\big(2 + (1+\gamma)(\delta+2)\big)}{2(1+2\gamma)\big(\sqrt{\zeta} + \sqrt{\eta}\big)^3}.$$

□

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