An Optimal Response-Adaptive Design for Multi-treatment Clinical Trials with Circular Responses

Taranga Mukherjee, Rahul Bhattacharya, and Atanu Biswas

1 Introduction

In clinical trials, equal allocation for assignment of subjects to competing treatment arms has long been advocated by the medical practitioners to reflect the view of equipoise at the outset of the trial. But continuing the view of equipoise Rosenberger and Lachin (2002) balances the allocation among the treatments without making any distinction between the superior and inferior treatments. Such lack of distinction among treatments under consideration is naturally questionable from ethical point of view and suggests continuous monitoring coupled with dynamic allocation. A dynamic allocation procedure allows the experimenter to evaluate the treatments at intermediate stages of the trial and skews the allocation in favour of the treatment doing better of the trial based on the available data. If the available allocation and response data are used for the allocation of every incoming subject, the allocation is termed a response-adaptive allocation.

Most of the response-adaptive designs, available in the literature, are developed for two treatment trials and only a few are available for multiple treatments. Further, almost all the available response-adaptive designs are either for binary, categorical or conventional continuous (often termed "linear") treatment responses. But angular responses are the natural outcomes in the context of several biomedical studies (e.g. in orthopedics, ophthalmology, sports medicine). The usual (i.e. linear) contin-

T. Mukherjee (✉) · R. Bhattacharya
Department of Statistics, University of Calcutta, Kolkata, India
e-mail: tm.custat@gmail.com

R. Bhattacharya
e-mail: rahul_bhattya@yahoo.com

A. Biswas
Applied Statistics Unit, Indian Statistical Institute, Kolkata, India
e-mail: atanu@isical.ac.in

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uous probability distributions are, therefore, inappropriate to capture periodicity in a bounded domain Fisher (1993). Naturally, applying an allocation design for linear continuous responses for circular response trials is not only inappropriate but may lead to fallacious results. Despite several occurrences of circular data in clinical trials, application of response-adaptive allocation designs in trials involving circular responses has attracted less attention Atkinson and Biswas (2014). Further, designing a clinical trial should not only focus on the ethical requirements (i.e. assigning higher number of subjects to the eventually better treatment) but efficiency issues (e.g. making precise inference on treatment efficacy) are also equally important. Considering both the ethical and efficiency requirements within the same framework, Biswas et al. (2015) and Biswas et al. (2017) developed a two-treatment allocation design for circular response clinical trials, which is one of the earliest contributions in this class of allocation designs and is commonly known as an optimal response-adaptive allocation. But clinical trials may involve multiple treatments, and defining ethical and efficiency concerns in the presence of several treatments is met with different challenges. In the current work, we define appropriate ethics and efficiency measures assuming multiple treatments and derive an optimal allocation design by weighing such requirements in a sensible way. In Sect. 2, we develop the ethics and efficiency requirements for circular response models and considering a constrained optimization problem, derive the optimal target proportion. We provide the response-adaptive randomization to target the optimal proportion in practice along with related large sample results in Sect. 3. Small sample performance of the proposed design is investigated and compared with the "gold standard" equal allocation in detail in Sect. 4. In Sect. 5, we redesign a real clinical trial with circular outcome adopting the proposed allocation design. Some related and relevant issues are finally discussed in Sect. 6.

2 The Proposed Allocation Design

Consider a clinical trial with t (>2) competing treatments, where the patient outcome is circular in nature. Unlike linear responses , circular responses cannot be compared directly and hence identifying a "better" patient response requires further consideration. In fact, circular responses are periodic in nature and hence in circular set-up, the responses 20° and 340° are identical in effect. Consequently, fallacious conclusions may be reached if such responses are analysed using existing methods. To avoid such impediment, the comparison among circular treatment responses is made with respect to a preferred direction, which is treated as a reference point. In general, a preferred direction should be chosen by practitioners as per the requirement of the study. A preferred direction can be chosen in multiple ways. For example, in medical studies related to shoulder movement, it is usually seen that a perfect shoulder allows 90° of internal rotation (Jain et al. 2013), and the preferred direction should be taken as 90° in that context. However, preferred direction can also be data driven.

Once a preferred direction is set, intuitively, a treatment is promising if it produces responses near the preferred direction. Therefore, if μ_0 is set as the preferred direction in a clinical trial, the quality of a response is determined by an appropriate distance from the preferred direction. Due to the periodic nature of circular responses, the linear deviation of the responses from the preferred direction yields little or no sense. We, therefore, use a circular distance measure Jammalamadaka and SenGupta (2001) defined by smaller of the two arc lengths between the preferred angle and the response angle along the circumference of an unit circle. Analytically, the circular distance between an arbitrary circular response ψ and preferred direction μ_0 can be expressed as $d(\psi, \mu_0) = \min(\psi - \mu_0, 2\pi - \overline{\psi - \mu_0})$ (see, Jammalamadaka and SenGupta (2001), for example). The distance d is a linear quantity having no periodicity and hence can be ordered conventionally. However, we have kept the preferred direction at 0°, throughout the work for the sake of brevity.

Since the aim of the current work is to develop allocation designs considering both ethics and efficiency, we need appropriate measures of both. For ethics, we introduce a clinically meaningful threshold "c", the distance above which is regarded as a treatment failure. Specifically, an observed response ψ is regarded beneficial if $d(\psi, 0) \leq c$. Therefore, if we consider a hypothetical non-randomized clinical trial with t treatments and n_k assignments to treatment k, the expected total number of benefited subjects is

$$\sum_{k=1}^{t} n_k P\{d(Y_k, 0) \leq c\}$$

where Y_k represents the responses to treatment k. Naturally, a higher value of the above or equivalently a lower value of $H(n_1, n_2, \ldots n_t) = \sum_{k=1}^{t} n_k P\{d(Y_k, 0) > c\}$ is desirable from an ethical perspective.

However, to measure the efficiency, we consider A optimality ((Silvey, 1980)) based on the large sample dispersion matrix of $(d(\tilde{\mu_1}, 0), d(\tilde{\mu_2}, 0), \ldots, d(\tilde{\mu_t}, 0))^T$, where $\tilde{\mu_k}$ is an estimator of μ_k under the non-randomized allocation. The large sample dispersion matrix takes the form $Diag(\frac{\sigma_1^2}{n_1}, \frac{\sigma_2^2}{n_2}, ..., \frac{\sigma_t^2}{n_t})$, with $\frac{\sigma_k^2}{n_k}$ as the large sample variance of $d(\tilde{\mu_k}, 0)$. Then, A optimality criterion dictates to use $\sum_{k=1}^{t} \frac{\sigma_k^2}{n_k}$ as an efficiency measure, where a lower value indicates higher precision of estimators. Thus, we suggest to obtain the optimal proportion $\rho_k = \left(\frac{n_k}{\sum_{j=1}^{t} n_j}\right)_{opt}$ to treatment k by solving the constrained optimization problem:

$$\begin{aligned} &\text{Minimize } \textstyle\sum_{k=1}^{t} \frac{\sigma_k^2}{n_k}, \\ &\text{subject to } \textstyle\sum_{k=1}^{t} n_k P(d(Y_k, 0) > c) < h \end{aligned}$$

for some $h > 0$. Application of standard optimization techniques ((Bazaraa et al., 2006)) expresses the optimal proportion as

$$\rho_k = \frac{\frac{\sigma_k}{\sqrt{\gamma_k}}}{\sum_{k=1}^{t} \frac{\sigma_k}{\sqrt{\gamma_k}}}, k = 1, 2, \ldots t.$$

where $\gamma_k = P\{d(Y_k, 0) > c\}$.

3 Implementation of the Allocation Design in Practice

The optimal target allocation function ρ_k is naturally a function of the parameters of the response distribution, and hence implementation requires knowledge of such unknown quantities. But these unknown parameters (say, θ) are never known in advance. Hence, we suggest to design the trial adaptively; that is, we suggest to use the currently available response and allocation data to estimate θ. In adaptive allocation, initially n_0 subjects are allocated to each of the t treatment arms, then responses from tn_0 subjects are obtained and based on that information the allocation probability for $(tn_0 + 1)$th subject is calculated. Naturally, this initial allocation n_0 is kept lower to assign more subjects adaptively.

Suppose $\delta_{k,i}$ is the treatment indicator taking the values 1 or 0 accordingly as the ith subject is assigned treatment k or not, and $\mathcal{F}_i$ indicates the information contained in the allocation-and-response data obtained up to and including the ith subject. Then, the $(i + 1)$th subject is assigned to treatment k with probability

$$P(\delta_{k,i+1}|\mathcal{F}_i) = \rho_k(\widehat{\boldsymbol{\theta}}^{(\boldsymbol{i})}),$$

where $\rho_k(\widehat{\boldsymbol{\theta}}^{(\boldsymbol{i})})$ is a strongly consistent estimator of ρ_k based on the available data up to and including the ith subject. In practice, we use sequentially updated maximum likelihood estimators and plug it into the allocation function at every stage to calculate the allocation probabilities.

Since for any allocation design, primary concern is ethics, we study the behaviour of the observed proportion of allocation to different treatments. If we denote the number of allocations by the proposed design to treatment k out of n assignments by $N_{kn} = \sum_{i=1}^{n} \delta_{k,i}$, the observed allocation proportion to treatment k is simply $\frac{N_{kn}}{n}$. Then under certain widely satisfied restrictions Hu et al. (2004) on the response distribution and continuity of $\rho_k(\theta_1, \theta_2, \ldots, \theta_k)$ in each of its arguments for every $k = 1, 2, \ldots, t$, we have the following result.

Result: As $n \to \infty$

$$\frac{N_{kn}}{n} \to \rho_k(\boldsymbol{\theta})$$

almost surely for each k = 1,2, …t

4 Performance Evaluation

4.1 Performance Measures

Performance of any allocation design needs to be assessed in the light of both ethics and optimality. An allocation function exhibits strong ethical perspective if it allocates higher number of patients to the better performing treatment arm. In this context, the expected allocation proportions (EAPs), defined by $E(\frac{N_{kn}}{n})$, $k = 1, 2, \ldots, t$, can be regarded as a measure of ethics, where the higher the value of EAP for better performing treatment arm is the indicator for ethical impact of the allocation design. Again to measure efficiency, we use the power of a relevant test of equality of treatment effects. But the concerned test is not a simple adaptation of the usual test of homogeneity for linear responses. In fact, for circular responses if μ_k is the mean direction associated with the kth treatment, then treatments j and k are equally effective if $d(\mu_k, 0) = d(\mu_j, 0)$ or equivalently if $\mu_k = \mu_j (\mod 2\pi)$ or $\mu_k = 2\pi - \mu_j (\mod 2\pi)$. However, the distance functions are linear in nature, and hence as an alternative, we consider testing the null
$H_0 : d(\mu_1, 0) = d(\mu_2, 0) = \cdots d(\mu_t, 0)$ against the alternative H_1 : at least one inequality in H_0.

Assuming treatment 1 as experimental and others as existing, we define the contrast-based homogeneity test statistic

$$T_n = (\mathbf{H}\hat{\mathbf{d}})^T \left[\mathbf{H}\hat{\Sigma}_{\hat{\mathbf{d}}}\mathbf{H}^T\right]^{-1} (\mathbf{H}\hat{\mathbf{d}}),$$

where

$$\hat{\mathbf{d}}^{t\times 1} = \begin{pmatrix} d(\hat{\mu}_1, 0) \\ d(\hat{\mu}_2, 0) \\ \vdots \\ d(\hat{\mu}_t, 0) \end{pmatrix},$$

$$\mathbf{H}^{\bar{t-1}\times t} = \begin{bmatrix} 1 & -1 & 0 & \cdots & 0 \\ 1 & 0 & -1 & \cdots & 0 \\ \vdots & \vdots & \ddots & \vdots & \\ 1 & 0 & 0 & \cdots & -1 \end{bmatrix},$$

$\hat{\Sigma}_{\hat{d}}$ is the estimated dispersion matrix of $\hat{d}^{t\times 1}$, and $\hat{\mu}_k$ is a strongly consistent estimator of μ_k based on n observations, generated through the proposed adaptive allocation design. Naturally, larger value of T_n indicates departure from the null hypothesis and hence a right tailed test based on T_n is appropriate to test H_0 against H_1.

4.2 Simulation Studies

In order to evaluate performance of the proposed optimal allocation design, we consider three treatments, namely 1, 2 and 3, and keep treatment 1 as the superior one (i.e. having minimum circular distance from preferred direction 0°) followed by treatments 2 and 3. Specifically, we assume that the response distribution for treatment j is von Mises with mean direction μ_j and concentration κ_j, $j = 1, 2, 3$. Naturally, μ_1 is kept closest to 0°. However, the concentration parameters κ_1, κ_2 and κ_3 are varied accordingly. Three sets of concentration parameters are considered separately. First, all treatment arms are assumed to have equal concentrations, then higher concentration is assigned to the superior treatment arms and finally higher concentration is assigned to inferior treatment arm. Considering different configurations of (μ_1, μ_2, μ_3) and $(\kappa_1, \kappa_2, \kappa_3)$, we conduct a simulation study with 25,000 iterations. The simulation is carried out for both the choices $n = 60$ and $n = 240$. For $n = 240$, the initial equal allocation n_0 is kept as 10, and for $n = 60$ the same is kept at 3. However for evaluation, the threshold value is fixed at $c = 30°$

Since the power of the concerned test under equal allocation is often considered as a benchmark, the power under the proposed optimal allocation is compared with that of equal allocation, where each treatment is assigned with equal probability. The details of expected allocation proportion (EAP) and power are reported in Tables 1 and 2. The performance figures in Tables 1 and 2 indicate that the allocation function successfully assigns a larger number of subjects to the superior treatment arm keeping the power almost as good as that of equal allocation. Also, the corresponding standard

Table 1 Expected allocation proportion and power for $n = 60$

$\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3$	EAP(SD)			Power	
	1	2	3	Proposed	Equal
(5, 5, 5, 2.0, 2.0, 2.0)	0.333(0.09)	0.333(0.09)	0.333(0.09)	0.050	0.050
(5, 10, 15, 2.0, 2.0, 2.0)	0.345(0.09)	0.331(0.07)	0.322(0.08)	0.141	0.118
(5, 15, 25, 2.0, 2.0, 2.0)	0.348(0.07)	0.332 (0.07)	0.318(0.08)	0.324	0.814
(5, 30, 45, 2.0, 2.0, 2.0)	0.366 (0.07)	0.323(0.08)	0.310 (0.09)	0.833	0.810
(5, 45, 60, 2.0, 2.0, 2.0)	0.370(0.07)	0.318(0.07)	0.311 (0.08)	0.975	0.097
(5, 75, 90, 2.0, 2.0, 2.0)	0.377 (0.07)	0.311 (0.07)	0.313(0.07)	1.000	1.000
(5, 5, 5, 1.0, 2.0, 2.0)	0.434(0.07)	0.288 (0.07)	0.280(0.06)	0.05	0.05
(5, 10, 15, 1.0, 2.0, 2.0)	0.439(0.08)	0.282 (0.07)	0.277 (0.08)	0.070	0.090
(5, 30, 45, 1.0, 2.0, 2.0)	0.462 (0.08)	0.275 (0.08)	0.261(0.08)	0.420	0.248
(5, 45, 60, 1.0, 2.0, 2.0)	0.472 (0.07)	0.267(0.07)	0.260 (0.07)	0.778	0.664
(5, 75, 90, 1.0, 2.0, 2.0)	0.474 (0.07)	0.262(0.07)	0.263 (0.07)	0.993	0.969
(5, 5, 5, 2.0, 2.0, 1.0)	0.292(0.07)	0.280 (0.07)	0.424(0.07)	0.050	0.050
(5, 15, 25, 2.0, 2.0, 1.0)	0.311(0.08)	0.276(0.08)	0.411(0.07)	0.203	0.112
(5, 30, 45, 2.0, 2.0, 1.0)	0.311(0.07)	0.276(0.06)	0.414(0.07)	0.530	0.269
(5, 45, 60, 2.0, 2.0, 1.0)	0.317(0.08)	0.267(0.06)	0.411(0.07)	0.800	0.634
(5, 75, 90, 2.0, 2.0, 1.0)	0.317(0.07)	0.268(0.07)	0.419(0.07)	0.985	0.991

Table 2 Expected allocation proportion and power for $n = 240$

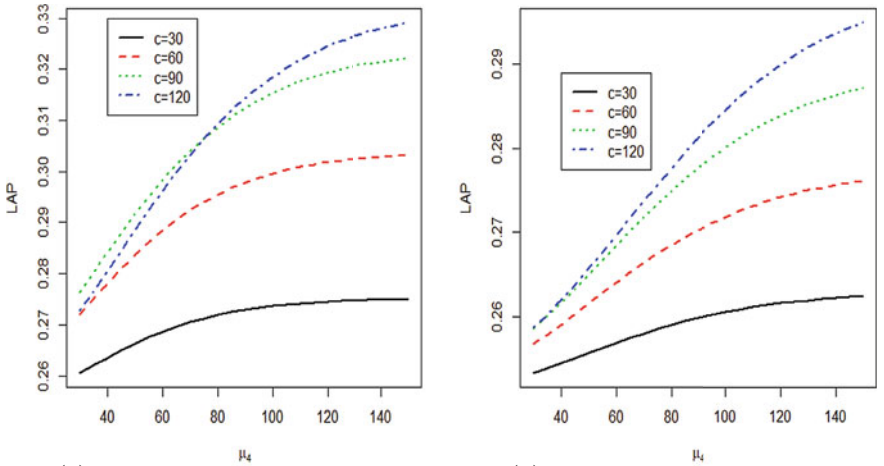
$\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3$	EAP(SD)			Power	
	1	2	3	Proposed	Equal
(5, 5, 5, 2.0, 2.0, 2.0)	0.333(0.04)	0.333(0.05)	0.333(0.04)	0.050	0.050
(5, 10, 15, 2.0, 2.0, 2.0)	0.342(0.04)	0.334(0.04)	0.323(0.04)	0.339	0.355
(5, 15, 25, 2.0, 2.0, 2.0)	0.352(0.03)	0.331(0.04)	0.316(0.04)	0.816	0.855
(5, 30, 45, 2.0, 2.0, 2.0)	0.365(0.05)	0.323(0.04)	0.311(0.04)	1.000	1.000
(5, 5, 5, 1.0, 2.0, 2.0)	0.458(0.04)	v.272(0.05)	0.278(0.05)	0.050	0.050
(5, 10, 15, 1.0, 2.0, 2.0)	0.468(0.05)	0.269(0.05)	0.262(0.04)	0.130	0.060
(5, 30, 45, 1.0, 2.0, 2.0)	0.491(0.04)	0.258(0.05)	0.249(0.04)	0.987	0.944
(5, 45, 60, 1.0, 2.0, 2.0)	499(0.04)	0.252(0.05)	0.247(0.04)	1.000	1.000
(5, 5, 5, 2.0, 2.0, 1.0)	0.270(0.04)	0.266(0.04)	0.458(0.07)	0.050	0.050
(5, 15, 25, 2.0, 2.0, 1.0)	0.283(0.04)	0.268(0.05)	0.447(0.05)	0.597	0.510
(5, 30, 45, 2.0, 2.0, 1.0)	0.294(0.04)	0.260(0.05)	0.445(0.04)	0.983	0.982
(5, 45, 60, 2.0, 2.0, 1.0)	0.299(0.05)	0.255(0.04)	0.445(0.05)	1.000	1.000

deviations, measuring the allocation fluctuation (reported in the parenthesis in the tables), remain significantly lower irrespective of the chosen sample sizes. All these facts make the proposed optimal allocation rule a competent one.

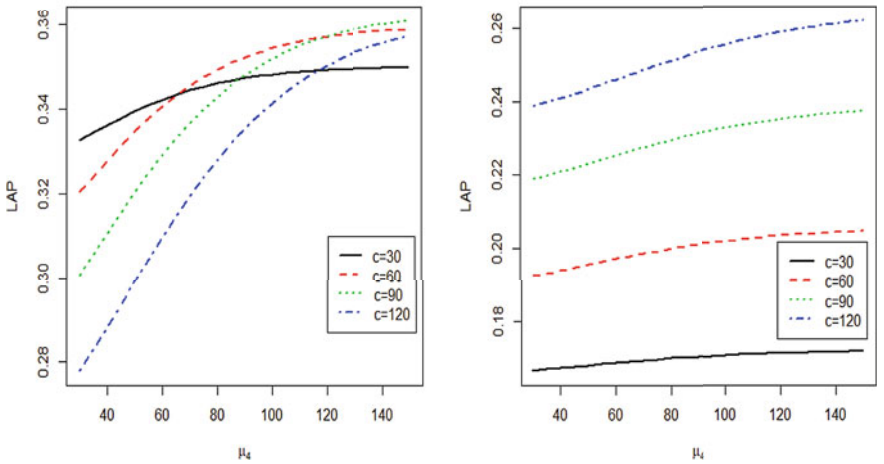
We further have studied the performance of the proposed allocation design considering four treatments based on limiting allocation proportion (LAP) by varying the threshold value c. LAP essentially indicates the theoretical limiting proportion of number of subjects allocated to a certain treatment arm to the total number of subjects available. The mean direction parameters for treatments 1, 2 and 3 are kept at 5°, 15° and 25°, respectively, and mean direction for treatment 4; i.e. μ_4 is varied from 25° to 160°. Thus, treatments 1, 2 3 and 4 can be regarded as ordered from superior to inferior. Naturally for a sensible allocation design limiting allocation proportion to treatment 1 should increase as μ_4 drifts away from 25°. In Fig. 1, we plot LAP to treatment 1 (i.e. the superior treatment) for varying μ_4 and various choices of $(\kappa_1, \kappa_2, \kappa_3, \kappa_4)$. The plot in Fig. 1 is found to be in agreement with the anticipated behaviour of LAP across various choices of c and $(\kappa_1, \kappa_2, \kappa_3, \kappa_4)$

5 Redesigning a Real Clinical Trial: SICS Trial

Now to evaluate the proposed procedure from a real clinical perspective, we consider a real trial on small incision cataract surgery (Bakshi 2010). We take into account three competing treatments, namely snare technique (see Basti 1993), irrigating vectis technique (see Masket 2004) and torsional phacoemulsification (see Mackool and Brint 2004) based on 19, 18 and 16 observations, respectively. Responses corresponding to each treatment are circular in nature, and hence the trial is appropriate to



(a) $\kappa_1 = 2, \kappa_2 = 2, \kappa_3 = 2, \kappa_4 = 2$ (b) $\kappa_1 = 1, \kappa_2 = 1, \kappa_3 = 1, \kappa_4 = 1$



(c) $\kappa_1 = 1, \kappa_2 = 1, \kappa_3 = 2, \kappa_4 = 2$ (d) $\kappa_1 = 2, \kappa_2 = 2, \kappa_3 = 1, \kappa_4 = 1$

Fig. 1 Limiting allocation proportion von Mises response for four treatments

judge the performance of the proposed allocation. The responses obtained from these three types of surgical interventions, namely snare, irrigating vectis and torsional phacoemulsification techniques, are assumed to follow von Mises with parameters (μ_s, κ_s), (μ_v, κ_v) and (μ_t, κ_t), respectively, and rationale behind such assumption is verified by Watson's goodness of fit test Mardia and Jupp (2004). In the light of this three independent competing treatments, the proposed allocation design is redesigned with the following parameter choices, estimated from the available data points.

Table 3 Allocation to different treatment arms

Treatment	EAP(SD)	
	Proposed	Actual
Snare	0.250(0.07)	0.358
Irrigating vectis	0.201(0.08)	0.339
Torsional phacoemulsification	0.548(0.08)	0.301

For the snare technique, parameters are estimated as $\hat{\mu}_s = 20.67°$, $\hat{\kappa}_s = 1.59$; for irrigating vectis, these estimates are $\hat{\mu}_v = 52.71°$, $\hat{\kappa}_v = 1.27$; for torsional phacoemulsification, the estimates of the parameters are $\hat{\mu}_t = 2.29°$, $\hat{\kappa}_t = 4.99$, respectively. As far as distance from preferred direction is concerned, torsional phacoemulsification appears to be much better than its competitors followed by snare's technique. In addition, torsional phacoemulsification has significantly higher concentration over others. Thus, the treatment clearly emerges as the best one. From Tables 3 and 4, we find that the proposed optimal allocation design produces about 23% higher EAP to the superior treatment torsional phacoemulsification and reduced the EAP for the other treatments as compared to the original allocation. This naturally shows the ethical impact of the proposed optimal response-adaptive allocation and hence makes the proposed allocation desirable in real clinical trial.

6 Concluding Remarks

The current work develops an optimal treatment allocation design for multiple arms by minimizing total number of treatment failures subject to fixed precision. Although essence of the proposed design is based on ethical point of view, the optimality of inference of treatment effect detection is not compromised. In fact, it is well competing with equal allocation design. However, no covariate effect is studied here, which is left for future consideration.

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