Journal of the Korean Statistical Society 48 (2019) 524–536

Contents lists available at ScienceDirect

Journal of the Korean Statistical Society

journal homepage: www.elsevier.com/locate/jkss

Multi-arm response-adaptive designs for circular responses

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ARTICLE INFO

Article history:
Received 24 December 2017
Accepted 26 March 2019
Available online 17 April 2019

AMS 2010 subject classifications:
primary 62L05
secondary 62P10

Keywords:
Response adaptive design
Circular responses

ABSTRACT

A multi-arm response-adaptive allocation design is developed for circular treatment outcomes. Several exact and asymptotic properties of the design are studied. Stage-wise treatment selection procedures based on the proposed response-adaptive design are also suggested to exclude the worse performing treatment(s) at earlier stages. Detailed simulation study is carried out to evaluate the proposed selection procedures. The applicability of the proposed methodologies is illustrated through a real clinical trial data on cataract surgery.

1. Introduction

The primary concern of any clinical trial is to maintain ethics while allocating subjects to different treatments under study especially when human lives are involved as experimental units. A response adaptive design uses the available allocation and response data and assigns a greater fraction of subjects to the treatment performing better. But the myopic strategy of favouring the better performing treatment causes imbalance in treatment allocation and eventually leads to a loss in power of a concerned statistical test. A loss in power not only reduces the treatment effect discrimination ability but also increases the trial size. Increased trial size increases the number of assignments to the inferior treatments and hence reduces the ethical impact. Therefore, a reasonable allocation design must consider ethics (i.e. favouring the better treatment for further allocation) as well as efficiency (i.e. high discrimination ability to identify a departure from the equality of treatment effects). A detailed description of related aspects can be found in the book length treatments (Atkinson & Biswas, 2014; Baldi Antognini & Giovagnoli, 2015)

However, most of the response adaptive designs, available in 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, or for conventional continuous (often termed "linear") treatment responses. But angular responses are natural outcome in the context of several biomedical studies (e.g. in orthopaedics and ophthalmology). The usual (i.e. linear) continuous probability distributions fail to model circular data due to their bounded domain and periodicity and hence makes the analysis of circular data significantly different from that of linear data (Fisher, 1993; Jammalamadaka & SenGupta, 2001). Naturally, applying an allocation design for linear continuous responses circular response trials, is not only inappropriate but may also lead to ambiguity.

Despite several occurrences of circular data in several clinical trials, there is scanty literature on response-adaptive allocation designs involving circular responses. Considering both the ethical and efficiency issues within the same

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https://doi.org/10.1016/j.jkss.2019.03.005
1226-3192/

framework, a two treatment allocation design for circular response, perhaps the earliest in literature is found in Biswas, Dutta, Laha, and Bakshi (2015). Specifically, the allocation design was developed by minimizing the total number of failures subject to a fixed precision, where circular responses are categorized as success or failure by means of a relevant cut off. But setting a cut off often incorporates subjectivity and discards information. Consequently, in a later work Biswas, Bhattacharya, and Mukherjee (2017) introduced the concept of a "better treatment" by avoiding any cut off based categorization for treatments producing circular outcomes. The definition of better treatment depends on the circular distance from a preferred direction; the lower is the distance, the better the treatment and hence avoids subjectivity. The allocation design of Biswas et al. (2017) is invariant to the choice of circular distance function and hence, works well for any circular response distribution.

In the current work, extending the notion of a "better treatment" to multiple treatment scenario, we introduce the concept of a "most promising" treatment and suggest an allocation function for multi treatment circular responses trials in Section 2. The response adaptive implementation of the derived allocation function in real situations together with related large sample result is discussed in Section 3. Section 4 explores the theoretical as well as empirical properties of the proposed design in extensive detail. Redesigning results of a real clinical trial adopting the proposed allocation is also added in Section 4. Again in multi-treatment trials, often the goal is to select the treatment arm which outperforms other treatment arms. However with multiple treatments, treatment selection procedures are available for binary and continuous responses (Atkinson & Biswas, 2014; Bandyopadhyay & Biswas, 1999, 2002) only. Therefore, in Section 5, we suggest and evaluate a treatment selection procedure using response adaptive randomization in stages, in which the less promising treatments are dropped in stages until a single treatment emerges as the winner. Finally, Section 6 summarizes the findings of the current work with a discussion on related and upcoming issues.

2. The proposed allocation designs

Consider a clinical trial with $t\ (>2)$ competing treatments. Let Y_k denote a typical response from a patient treated by the kth treatment, where the response is circular in nature and hence has a distribution belonging to some circular family of distributions, k = 1,2,..t. As circular data is periodic in nature, such observations cannot be compared with each other numerically. Therefore, if the response is circular, a treatment producing conventionally higher (or lower) response cannot be declared as "promising". In fact, fallacious conclusions may be reached if such responses are analysed using existing methods. To circumvent this problem, the comparison among circular treatment responses can be made with respect to a reference point, called the preferred direction. A preferred direction is often set by the practitioners according to the requirement of the study. For example, in medical studies related to shoulder movement, it is usually seen that a perfect shoulder allows 90° of internal rotation (Jain, Wilcox III, Katz, & Higgins, 2013), and the preferred direction should be taken as 90° in that context. Intuitively, a treatment is promising if it produces responses near the preferred direction.

Specifically, if μ_0 is the known preferred direction for a certain clinical trial, a response closer to μ_0 is considered to be the desired one. Naturally, the quality of a response is determined by the distance from the preferred direction. Since the circular responses are not just numerical values but directions, simple subtraction of a response from the preferred value would not give a meaningful distance measure . We, therefore, use a circular distance measure (Jammalamadaka & SenGupta, 2001) defined by smaller of the two arc-lengths between the preferred angle and the response angle along the circumference of a 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 & SenGupta, 2001, for example). The distance d is a linear quantity having no periodicity and hence can be ordered conventionally.

Thus based on the distance criterion "d", for two treatments (1 and 2), treatment 1 is more promising than treatment 2 if we have $d(Y_1, \mu_0) < d(Y_2, \mu_0)$ stochastically. Extending the idea for multiple treatments, kth treatment can be considered as most promising if the corresponding distance metric $d(Y_k, \mu_0)$ is stochastically the least, that is, if $d(Y_k, \mu_0) < \min_{1\le j(\neq k)\le t} d(Y_j, \mu_0)$ stochastically. On the contrary, treatment k is considered to be least promising if $d(Y_k, \mu_0)$ is stochastically the highest.

Being consistent with the notion of a promising treatment, we, therefore suggest the allocation probability for treatment k as,

$$\rho_k = P\left\{ d(Y_k, \mu_0) < \min_{1\le j(\neq k)\le t} d(Y_j, \mu_0) \right\}, k = 1, 2, ..t.$$

Naturally, $\sum_{k=1}^{t} \rho_k = 1$ and if the treatments are equally promising or equivalently if $d(Y_k, \mu_0), k = 1, 2, \ldots, t$ are independently and identically distributed then $\rho_k = \frac{1}{t}$, for every k. Moreover, if treatment k is most promising, stochastic ordering ensures $\rho_k > \frac{1}{t}, k = 1, 2, ..t..$ Hence the suggested allocation function ρ_k is capable of assigning larger number of subjects to the better performing treatment arm. Further, it is worth mentioning that the criterion of promising treatment remains valid for any circular response distribution. However, for the rest of the development, we set μ_0 at 0° and derive the analytic expression of ρ_k in the following lemma, the proof of which given in the Appendix.

Lemma. *If F_j and f_j denote respectively the cumulative distribution function and density function corresponding to a circular random variable Y_j, representing response from the jth treatment arm, $j = 1, 2, \ldots, t$, then*

$$\rho_k = \int_0^{\pi} \prod_{j(\neq k)=1}^{t} G_j(y) f_{Y_k}(y) dy - \int_{\pi}^{2\pi} \prod_{j(\neq k)=1}^{t} G_j(y) f_{Y_k}(y) dy,$$

where $G_j(y) = F_{Y_j}(2\pi - y) - F_{Y_j}(y)$.

However, $d^*(\psi, \mu_0) = 1 - \cos(\psi - \mu_0)$ is often used as an alternative distance measure between ψ and μ_0 (Jammalamadaka & SenGupta, 2001, p. 16). Interestingly, $d(Y_j, 0) > d(Y_k, 0)$ is equivalent to $d^*(Y_j, 0) > d^*(Y_k, 0)$ for any (Y_j, Y_k), and hence, we essentially get the same allocation function even if the alternative distance metric d^* is used. Thus, without any loss of generality, we continue with the former distance metric assuming $\mu_0 = 0°$.

3. Implementation of the allocation design in practice

The allocation function ρ_k, defined in the earlier section, involves unknown parameters of the response distribution. If $\boldsymbol{\theta_k}$ is the d-dimensional parameter vector corresponding to the kth treatment response variable Y_k, then the allocation function can be expressed as, $\rho_k = \rho_k(\boldsymbol{\theta})$, where $\boldsymbol{\theta} = (\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \ldots, \boldsymbol{\theta}_t)^T$. As data is obtained in each stage of the trial, sequentially updated parameter estimates are plugged into the allocation function under consideration to determine the allocation probabilities of the next subject. However, initially each of the treatment arms is assigned with n_0 subjects and parameters are estimated from the available data. Then the response-adaptive strategy starts from the $(tn_0 + 1)$th subject onwards.

Let $\delta_{k,i}$ be the treatment indicator taking the values 1 or 0 according to as the ith subject is assigned treatment k or not, and $\mathcal{F}_i$ be the sigma algebra generated by the allocation-and-response data obtained up to and including the ith subject. Then, the $(i + 1)$st 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. We suggest to use sequentially updated maximum likelihood estimators at each stage to modify the allocation probabilities dynamically. In particular for the (i+1)th subject, we suggest to estimate θ by solving the likelihood equation, $\frac{\partial \ell_i(\boldsymbol{\theta})}{\partial \boldsymbol{\theta}} = 0$, where $\ell_i(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \ldots, \boldsymbol{\theta}_t) = \prod_{j=1}^{i} \prod_{k=1}^{t} \{f_k(y_{kj}, \boldsymbol{\theta}_k)\}^{\delta_{k,j}}$ is the likelihood of the data after i responses are obtained with y_{kj} as the response of the jth subject to treatment k.

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 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 $\frac{N_{kn}}{n}$. Now for an assessment of such a proportion in the limit, we impose the following restrictions on the response distribution $f_k(., \boldsymbol{\theta}_k)$ and allocation function $\rho_k(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \ldots, \boldsymbol{\theta}_t)$, $k = 1, 2, ..t$.

C1. There exists an open subset ω of the parameter space Ω containing the true parameter.
C2. The integral $\int f_k(y, \boldsymbol{\theta}_k) dy$ is twice differentiable with respect to θ_k under the integral sign and the first order partial derivative of the likelihood function has finite moments order n for some $n > 2$.
C3. The likelihood $\ell_i(\boldsymbol{\theta})$ admits all third order partial derivatives and such a derivative is bounded by some integrable function for all $\boldsymbol{\theta} \in \omega$.
C4. $\rho_k(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, \ldots, \boldsymbol{\theta}_t)$ is continuous in each of its arguments for every k = 1,2,..t.

Then we have the following result.

Result. *Under the conditions C1–C4 above, as $n \to \infty$*

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

almost surely for each k = 1,2,..t

Proof. Since $N_{1n} + N_{1n} + \cdots + N_{kn} = n$, under conditions C1–C4, we get that as $n \to \infty$, $N_{kn} \to \infty$ almost surely for each $k = 1, 2, ..t$. Consequently, as $n \to \infty$ $\hat{\boldsymbol{\theta}}^{(n)} \to \boldsymbol{\theta}$ almost surely.

Now consider the representation,

$$\frac{N_{kn}}{n} = \frac{1}{n} \sum_{j=1}^{n} \{\delta_{k,j} - E(\delta_{k,j}|\mathcal{F}_{j-1})\} + \frac{1}{n} \sum_{j=1}^{n} \rho_k(\hat{\boldsymbol{\theta}}^{(j)}).$$

Then the first term on the right hand side of the above equation converges to zero almost surely as $n \to \infty$ by the martingale convergence theorem (Hall & Heyde, 1980). The second term converges almost surely to $\rho_k(\boldsymbol{\theta})$ as a consequence of strong consistency of the parameter estimators and condition C4. □

4. Performance evaluation of the allocation design

4.1. Performance measures

Performance evaluation of any allocation design has two aspects, namely ethics and efficiency. For most of the clinical trials, ethical benchmark is set on the basis of the distribution of the allocations to different treatments. Thus expected allocation proportions (EAP), defined by $E(\frac{N_{kn}}{n}), k = 1, 2, \ldots, t$ are indicators of the allocation design's ability to skew the allocation towards the better performing treatment. Therefore, for the ethics, we use expected allocation proportion (EAP) to different treatment arms. Again to measure efficiency, we use the power of a relevant test of equality of treatment effects. However such a test is not a simple adaptation of the usual test of homogeneity for linear responses. In the context of 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 $\mu_k = 2\pi - \mu_j(\mod 2\pi)$. Since, the distance functions are linear in nature, 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.

In order to perform the above test we assume treatment 1 as experimental and others as existing. Then motivated by the usual contrast based homogeneity test statistic, we define the following statistic

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

where

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

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

$\hat{\Sigma}_{\hat{d}}$ 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 some allocation design. Naturally larger value of T_n indicates departure from the null hypothesis.

Further, directional hypotheses are often used in confirmatory trials. Consequently, we consider one of such hypotheses and proceed using the framework of union intersection principle. Specifically, we consider treatment 1 as the experimental and the others existing. Then assuming the underlying response distribution for the jth treatment as a member of the circular family with mean direction μ_j, we consider testing equality of the treatment effects against the alternative that the experimental treatment is at least as good as the existing treatment. Thus we consider testing $H_0 : d(\mu_1, 0) = .. = d(\mu_t, 0)$ against $H_1 : d(\mu_1, 0) < d(\mu_j, 0)$, for at least one $j \neq 1$. Since the null hypothesis is the intersection of hypotheses $H_{0j} : d(\mu_j, 0) = d(\mu_1, 0), j = 2, \ldots, t$ and the alternative can be looked upon as the union of the hypotheses $H_{1j} : d(\mu_j, 0) > d(\mu_1, 0), j \neq 1$, we follow the union intersection principle of hypothesis testing. For testing H_{0j} against H_{1j}, we suggest to use the statistic,

$$W_j = \frac{d(\hat{\mu}_j, 0) - d(\hat{\mu}_1, 0)}{\sqrt{\frac{\hat{\sigma}_1^2}{N_{1n}} + \frac{\hat{\sigma}_j^2}{N_{jn}}}},$$

where, σ_j^2 is the asymptotic variance of $d(\hat{\mu}_j, 0)$ and $\widehat{\sigma}_j^2$ is the maximum likelihood estimator of $\sigma_j^2, j \neq 1$. Naturally, a right tailed test based on W_j is appropriate. Since rejection of $H_{0j}, j \neq 1$ indicates the rejection of the global null hypothesis H_0, we reject the global null hypothesis against the directional alternative if $W_n^* = \max_{j\neq 1} W_j$ is too large.

4.2. Competitors

Meaningful performance evaluation of any allocation design requires comparison of performance measure with existing allocation designs. We therefore, consider the following competitors.

As the first competitor, we consider the framework of Biswas and Coad (2005) and suggest an allocation design based on pairwise comparison. Note that superiority of treatment k can also be defined pairwise i.e. treatment k is superior if separately for every $j \neq k$, $d(Y_k, 0) < d(Y_j, 0)$ stochastically. Summing the probabilities of such events we get a treatment effectiveness measure for treatment k. Since the number of all such comparisons is $\binom{t}{2}$, we define the following allocation

probability for treatment k

$$\tau_k = \frac{1}{\binom{t}{2}} \sum_{j(\neq k)=1}^{t} P\left\{d(Y_k, 0) < d(Y_j, 0)\right\}$$
$$= \frac{1}{\binom{t}{2}} \sum_{j(\neq k)=1}^{t} \left[\int_0^{\pi} G_j(y)dy - \int_{\pi}^{2\pi} G_j(y)dy\right].$$

Naturally, $\tau_k = \frac{1}{t}$ for equally performing treatments and is more than $\frac{1}{t}$ if treatment k is the most promising. Moreover, the analytic expression of τ_k enables the allocation function to work for any circular distribution. We use response adaptive route for practical implementation and denote the allocation by τ rule.

However, a competitor, which is a trade off between ethics and efficiency, is not available in literature for multiple treatments under circular responses and hence we derive afresh. For the derivation we follow, the consideration in Biswas, Mandal, and Bhattacharya (2011) and Biswas et al. (2015) i.e. categorize the responses as success or failure using some clinically convenient threshold "c" but adopt the approach described in Baldi Antognini and Giovagnoli (2015). Specifically, a circular response "ψ" is considered as a success if $d(\psi, 0) < c$ for some clinically meaningful "c". Therefore, if we consider a hypothetical non-randomized multi-treatment set up, the expected proportion of failures is simply, $H(\pi_1, \pi_2, \ldots, \pi_t) = \sum_{k=1}^{t} \pi_k P\{d(Y_k, 0) > c\} = \sum_{k=1}^{t} \pi_k \gamma_k$, where, π_k is the proportion of allocation to treatment k and $\gamma_k = P\{d(Y_k, 0) > c\}$. Naturally, a lower value of the criterion H is desirable. However, to measure the efficiency, we consider A optimality (Silvey, 1980) based on the large sample dispersion matrix of $(d(\tilde{\mu_1}, 0), d(\tilde{\mu_2}, 0), \ldots, d(\tilde{\mu_t}, 0))$, where $\tilde{\mu}_k$ is an estimator of μ_k for fixed $\pi_k, k = 1, 2, \ldots, t$. Then the large sample dispersion matrix takes the form $Diag(\frac{\sigma_1^2}{\pi_1}, \frac{\sigma_2^2}{\pi_2}, \ldots, \frac{\sigma_t^2}{\pi_t})$, with $\frac{\sigma_k^2}{\pi_k}$ as the large sample variance of $d(\tilde{\mu_k}, 0)$. Then A optimality criterion dictates to use $\sum_{k=1}^{t} \frac{\sigma_k^2}{\pi_k}$ as an efficiency measure and we suggest to obtain the optimal proportion π_k^* to treatment k by solving the constrained optimization problem:

$$\text{Minimize} \sum_{k=1}^{t} \frac{\sigma_k^2}{\pi_k},$$
$$\text{Subject to} \sum_{k=1}^{t} \pi_k \gamma_k < h \text{ and } \sum_{k=1}^{t} \pi_k = 1$$

and for some $h > 0$. Before, we apply standard optimization techniques (Bazaraa, Sherali, & Shetty, 2006), some issues related to the choice of h need explanation. First of all, we note that $\sum_{k=1}^{t} \pi_k \gamma_k \in [\min_{1\leq k\leq t} \gamma_k, \max_{1\leq k\leq t} \gamma_k]$. Naturally, for any h exceeding $\max_{1\leq k\leq t} \gamma_k$, the restriction $\sum_{k=1}^{t} \pi_k \gamma_k < h$ is trivially satisfied and hence becomes redundant. In such a situation, we get the optimal solution $\pi_k^* = \frac{\sigma_k}{\sum_{k=1}^{t} \sigma_k}, k = 1, 2, 3, \ldots, t$. Specifically, optimal solution exists for any h exceeding $\min_{1\leq k\leq t} \gamma_k$ though it was not possible to express such a solution in a tractable form. However, no optimal solution exists for $h \leq \min_{1\leq k\leq t} \gamma_k$, and as a compromise, we suggest equal randomization (i.e. assigning each treatment with equal probability $\frac{1}{t}$) in such a situation. The resulting allocation is, therefore, far from a conventional optimal allocation, but provides a trade off between ethics and efficiency. For further consideration, we use response adaptive randomization and refer the resulting allocation as ρ^* rule.

In addition, we also consider equal randomization (indicated by Equal), where each treatment is assigned with equal probability $\frac{1}{t}$.

4.3. Simulation studies

In order to explore the performance characteristics of the proposed and competing allocation designs, we extensively use the von Mises distribution as the distribution of responses. In particular, we assume that the response variable Y_j is distributed as von Mises with mean direction μ_j and concentration parameter κ_j with the density function

$$\frac{1}{2\pi I_0(\kappa_j)} \exp\left\{\kappa_j \cos(y - \mu_j)\right\}, 0 < y \leq 2\pi,$$

where $0 \leq \mu_j \leq 2\pi$, $\kappa_j > 0$ and

$$I_p(\kappa_j) = \frac{1}{2\pi} \int_0^{2\pi} \exp(\kappa_j \cos y) \cos(py)dy$$

is the modified Bessel function of order $p \geq 0$. Then based on n observations, $Y_{ji}, i = 1, 2, \ldots, j = 1, 2, \ldots, t$, the maximum likelihood (ML) estimator $\hat{\mu}_j$ of μ_j satisfies $tan(\hat{\mu}_j) = \bar{S}_j/\bar{C}_j$, where $N_{jn}\bar{S}_j = \sum_{i=1}^{n} \delta_{ji} \sin Y_{ji}$ and $N_{jn}\bar{C}_j = \sum_{i=1}^{n} \delta_{ji} \cos Y_{ji}$. However, the ML estimator $\hat{\kappa}_j$ of κ_j is obtained numerically from the following equation

$$A(\hat{\kappa}_j) = (\bar{C}_j^2 + \bar{S}_j^2)^{1/2},$$

Table 1
EAP(SD) to different treatments for von Mises responses with $n = 60$.

$(\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3)$	EAP(SD)								
	ρ			τ			$\rho^*(h = 0.6)$		
	1	2	3	1	2	3	1	2	3
(5, 5, 5, 2.0, 2.0, 2.0)	.333(0.09)	.333(0.09)	.333(0.09)	.333(0.09)	.333(0.09)	.333(0.09)	.333(0.12)	.333(0.12)	.333(0.12)
(5, 10, 15, 2.0, 2.0, 2.0)	.342(0.09)	.332(0.09)	.324(0.10)	.338(0.09)	.330(0.07)	.331(0.08)	.354(0.12)	.335(.11)	.309 (.12)
(5, 15, 25, 2.0, 2.0, 2.0)	.344(0.10)	.351(0.09)	.304(0.10)	.342(0.09)	.338(0.07)	.319(0.08)	.374 (0.12)	.329(0.10)	.296(0.12)
(5, 30, 45, 2.0, 2.0, 2.0)	.426(0.10)	.320(0.09)	.253(0.10)	.387(0.08)	.336(0.09)	.275(0.08)	.432(0.12)	.299 (0.10)	.268(0.12)
(5, 45, 60, 2.0, 2.0, 2.0)	.485(0.10)	.287(0.10)	.227(0.10)	.415(0.08)	.312(0.08)	.272(0.08)	.430(0.12)	.286(0.11)	.283(0.12)
(5, 60, 75, 2.0, 2.0, 2.0)	.485(0.11)	.287(0.10)	.227(0.09)	.415(0.08)	.312(0.08)	.272(0.08)	.419 (0.12)	.292(0.12)	.287 (0.12)
(5, 75, 90, 2.0, 2.0, 2.0)	.631(0.11)	.214(0.10)	.154(0.09)	.465(0.09)	.305(0.08)	.229(0.08)	.427(0.10)	.281(0.12)	.291(0.12)
(5, 5, 5, 1.0, 2.0, 2.0)	.239(0.07)	.380(0.07)	.380(0.08)	.272(0.08)	.358(0.07)	.369(0.08)	.391(0.12)	.312 (0.09)	.295(0.12)
(5, 10, 15, 1.0, 2.0, 2.0)	.246(0.08)	.386(0.08)	.367(0.08)	.284(0.08)	.360(0.07)	.355(0.08)	.374(0.11)	.323 (0.12)	.302(.12)
(5, 15, 25, 1.0, 2.0, 2.0)	.277(0.08)	.383(0.08)	.338(0.08)	.296(0.08)	.363(0.07)	.340(0.08)	.366 (0.10)	.347(0.12)	.285 (0.11)
(5, 30, 45, 1.0, 2.0, 2.0)	.320(0.09)	.365(0.09)	.313(0.09)	.327(0,08)	.350(0.08)	.322(0.07)	.339 (0.13)	.373 (0.11)	.286 (0.12)
(5, 45, 60, 1.0, 2.0, 2.0)	.385(0.09)	.345(0.09)	.268(0.08)	.367(0.08)	.344(0.08)	.287(0.08)	.378 (0.12)	.327 (0.10)	.293 (0.11)
(5, 60, 75, 1.0, 2.0, 2.0)	.437(0.11)	.318(0.10)	.244(0.08)	.389(0.09)	.337(0.08)	.272(0.08)	.394 (0.12)	.305 (0.12)	.300(0.12)
(5, 75, 90, 1.0, 2.0, 2.0)	.507(.10)	.282(0.09)	.210(0.08)	.419(0.09)	.326(0.08)	.253(0.08)	.392 (0.12)	.307 (0.13)	.300(0.12)
(5, 5, 5, 2.0, 2.0, 1.0)	.369(0.10)	.363(0.10)	.267(0.09)	.356(0.08)	.365(0.09)	.278(0.09)	.396(.12)	0.396(.11)	0.206(.12)
(5, 10, 15, 2.0, 2.0, 1.0)	.392(0.11)	.361(0.09)	.246(0.09)	.366(0.09)	.363(0.08)	.270(0.09)	.401(.12)	.388(0.11)	.209(0.12)
(5, 15, 25, 2.0, 2.0, 1.0)	.376(0.09)	.373(0.09)	.249(0.08)	.367(0.08)	.358(0.08)	.274(0.08)	.412 (0.12)	.383(0.10)	.204(0.09)
(5, 30, 45, 2.0, 2.0, 1.0)	.442(0.09)	.338(0.09)	.219(0.08)	.395(0.07)	.351(0.08)	.252(0.09)	.428(0.11)	.373(0.12)	.198 (0.09)
(5, 45, 60, 2.0, 2.0, 1.0)	.483(0.10)	.305(0.08)	.210(0.08)	.412(0.08)	.339(0.08)	.248(0.08)	.433(0.12)	.366 (0.11)	.200 (0.09)
(5, 60, 75, 2.0, 2.0, 1.0)	.550(0.10)	.258(0.08)	.190(0.08)	.442(0.06)	.318(0.07)	.239(0.07)	.433(0.11)	.366(0.10)	.200 (0.08)
(5, 75, 90, 2.0, 2.0, 1.0)	.613(0.11)	.206(0.08)	.179(0.07)	.466(0.08)	.299(0.08)	.233(0.08)	.432 (0.12)	.366 (0.11)	.200 (0.09)

Table 2
EAP(SD) for different treatments for von Mises responses with $n = 240$.

$(\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3)$	EAP(SD)								
	ρ			τ			$\rho^*(h = 0.6)$		
	1	2	3	1	2	3	1	2	3
(5, 5, 5, 2.0, 2.0, 2.0)	.333(0.05)	.333(0.05)	.333(0.04)	.333(0.05)	.333(0.04)	.333(0.04)	.333(0.04)	.333(0.05)	.333(0.04)
(5, 10, 15, 2.0, 2.0, 2.0)	.342(0.04)	.334(0.05)	.323(0.03)	.339(0.04)	.333(0.04)	.326(0.03)	.366(0.06)	.319(0.07)	.313(0.05)
(5, 15, 25, 2.0, 2.0, 2.0)	.360(0.04)	.340(0.05)	.298(0.04)	.353(0.05)	.339(0.05)	.307(0.05)	.373(0.06)	.323(0.08)	.302(0.08)
(5, 30, 45, 2.0, 2.0, 2.0)	.420(0.04)	.331(0.04)	.248(0.05)	.391(0.04)	.336(0.04)	.271(0.04)	.387(0.07)	.308(0.08)	.303(0.07)
(5, 5, 5, 1.0, 2.0, 2.0)	.247(0.04)	.379(0.04)	.379(0.05)	.261(0.04)	.371(0.04)	.366(0.03)	.507(0.07)	.371 (0.08)	.371(0.06)
(5, 10, 15, 1.0, 2.0, 2.0)	.252(0.05)	.381(0.04)	.366(0.05)	.265(0.04)	.371(0.04)	.362(0.04)	.480(0.07)	.395(0.05)	.374(0.07)
(5, 15, 25, 1.0, 2.0, 2.0)	.262(0.04)	.385(0.05)	.352(0.04)	.272(0.05)	.371(0.04)	.355(0.04)	.432(0.06)	.442(0.07)	.375(0.06)
(5, 30, 45, 1.0, 2.0, 2.0)	.314(0.04)	.390(0.04)	.295(0.04)	.311(0.04)	.377(0.03)	.311(0.04)	.384(0.06)	.518(0.07)	.347(0.08)
(5, 45, 60, 1.0, 2.0, 2.0)	.375(0.03)	.362(0.04)	.261(0.04)	.353(0.03)	.359(0.04)	.287(0.04)	.424(0.07)	.415(0.08)	.410(0.08)
(5, 5, 5, 2.0, 2.0, 1.0)	.375(0.03)	.379(0.03)	.245(0.04)	.367(0.04)	.372(0.03)	.259(0.05)	.375 (0.07)	.385(0.07)	.488(0.07)
(5, 10, 15, 2.0, 2.0, 1.0)	382(0.04)	.376(0.04)	.240(0.04)	.373(0.05)	.371(0.03)	.255(0.04)	.394(0.06)	.385(0.07)	.470 (0.08)
(5, 15, 25, 2.0, 2.0, 1.0)	.394(0.03)	.371(0.03)	.233(0.04)	.381(0.04)	.367(0.03)	.250(0.04)	.408 (0.07)	.387(0.08)	.454(0.08)
(5, 30, 45, 2.0, 2.0, 1.0)	.438(0.04)	.344(0.04)	.217(0.04)	.407(0.04)	.355(0.04)	.237(0.05)	.562 (0.07)	.330 (0.07)	.357(0.08)
(5, 45, 60, 2.0, 2.0, 1.0)	.499(0.04)	.295(0.04)	.204(0.04)	.442(0.05)	.327(0.04)	.229(0.04)	.694(0.07)	.258(0.07)	.296 (0.06)

where $A(\kappa_j) = I_1(\kappa_j)/I_0(\kappa_j)$ (Mardia & Jupp, 2004, pp. 85, 86). Then under the von Mises assumption, we get

$$\hat{\sigma}_j^2 = \frac{1}{\hat{\kappa}_j A(\hat{\kappa}_j)}, j = 1, 2.., t.$$

However, for the simulation study, we consider t = 3 treatments and 10000 repetitions, where the data is generated according to the allocation designs, indicated earlier. For the simulation we consider n = 60 and n = 240. However, to run response adaptive rules (i.e. ρ, τ, ρ^*), we assign $n_0 = 3$ subjects to each treatment arm to get initial parameter estimates and then start the adaptive allocation from the tenth subject onwards.

In selecting the parameters for the simulation study, an ordering is maintained. The first treatment is considered to be the superior one followed by the second and the third. Initially equal concentration is assumed for the treatments. Then two sets of unequal concentration parameters are used. In the first case, higher concentration is attached to the better treatments, i.e. to the first and second treatments. In the second set, higher concentration is associated with the inferior treatments, that is, to the third and second treatments. Here μ_1 is fixed at 5° and μ_2 and μ_3 are varied as mentioned above. Expected allocation proportion (EAP) along with standard deviations (SD) is obtained for proposed and competing allocation designs considering $c = 30°$ and are reported in Tables 1 and 2.

Powers of the tests based on T_n and W_n^* at various alternatives are reported in Tables 3 and 4 for the allocation rules ρ, τ and ρ^* and are compared with those obtained under equal allocation. From Tables 1 and 2, it can be readily noted that for ρ and τ rules under equal concentration, allocation is uniformly skewed towards treatment 1. If higher concentration is assigned to treatments 1 and 2, larger number of subjects are allocated to them in comparison to equal concentration case. On the other hand, if lower concentration is attached with treatment 1, the EAP drops even if it has mean direction nearer to the preferred direction 0°. This is natural as lower concentration produces more responses far from the mean direction even if the mean direction is close to the preferred direction and hence the concerned EAP decreases. The optimal rule mimics the same behaviour except for the fact that under equal concentration, it only skews a moderate number of subjects to the better treatment arm in comparison to the other rules.

From the figures of Tables 3 and 4, we observe that the power (both contrast and multiple comparison based) increases rapidly for all the allocation rules. The powers obtained under skewed allocations are quite competitive with those obtained under equal allocation. A close look towards the results reveals that ρ rule gives slight edge to the τ rule as far as EAP values are concerned. On the other hand, the ρ^* rule is slightly more variable and produces similar EAP and power, in general. However, the performance of the ρ^* rule depends heavily on the choice of h. Theoretically, any sensible choice of h must lie in (0, 1). However, too small h causes the equal allocation to dominate whereas a significantly higher h makes the allocation close to Neyman optimal allocation. The more the degree of superiority (or inferiority) of the better (or worst) treatment, the higher (or lower) is the corresponding γ value. Since, we do not consider significantly different treatment arms in a clinical trial, in general, a choice of h around 0.5 is reasonable.

We also compute the type I error rates empirically. Since, under the null hypothesis T_n is asymptotically distributed as χ^2 with 2 degrees of freedom, we compute the probability $P_{H_0}\{T_n > \chi^2_{2;0.05}\}$, where $\chi^2_{2;0.05}$ denotes upper 5 percent point of chi square distribution with 2 degrees of freedom. We further investigate such requirement in the multiple comparison set up using the cut off based on the asymptotic null distribution of $\max(W_2, W_3)$. In particular, we empirically compute $P_{H_0}\{W_n^* > w\}$, where w is obtained from the asymptotic null distribution of W_n^*. Now, under the null hypothesis and von Mises assumption, the joint asymptotic distribution of (W_2, W_3) is standard bivariate normal with correlation coefficient

$$\frac{\sigma_1^2}{\sqrt{\sigma_1^2+\sigma_2^2}\sqrt{\sigma_1^2+\sigma_3^2}}$$

with $\sigma_j^2 = \frac{1}{\kappa_j A(\kappa_j)}$.

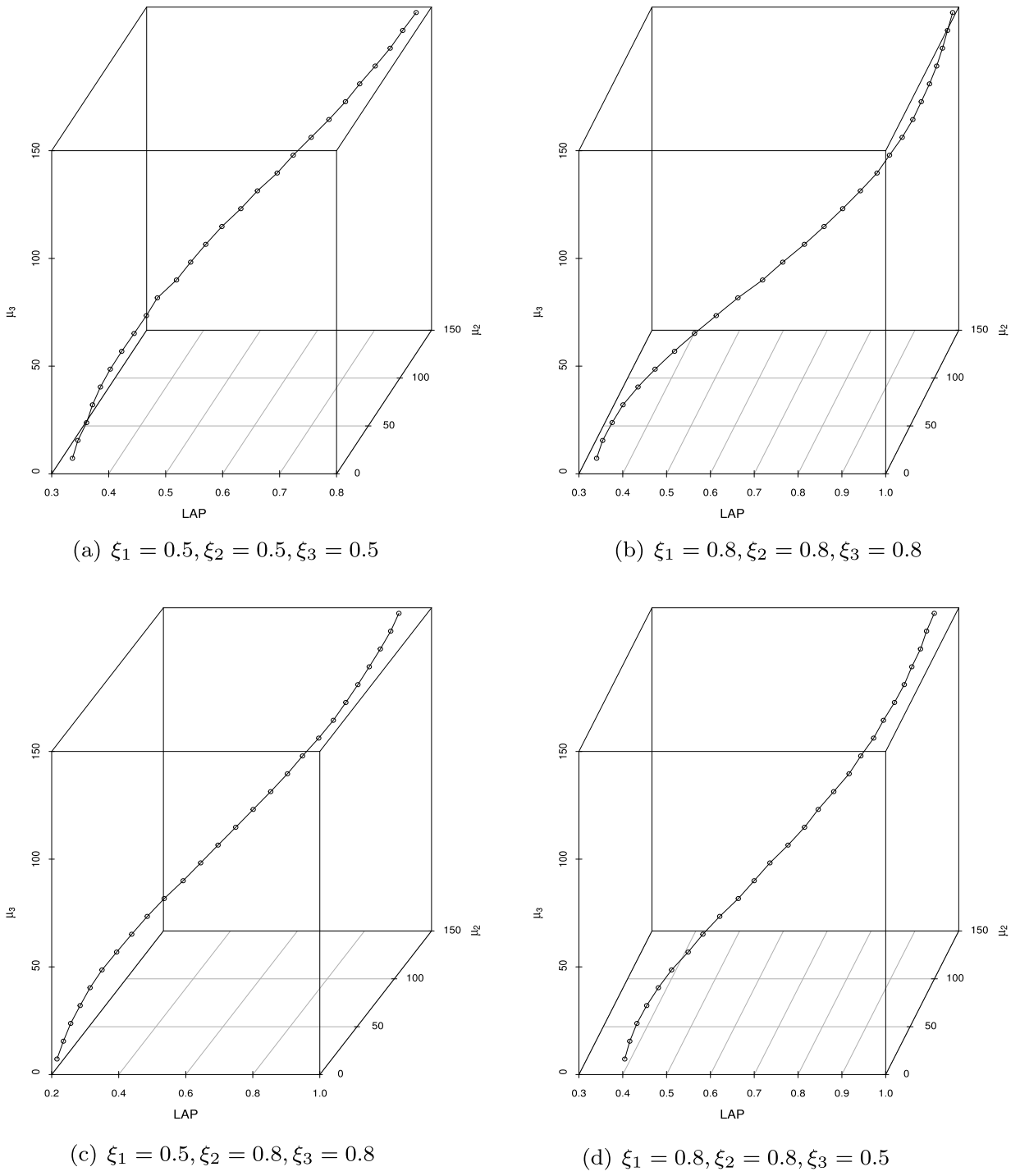
Considering different choices of $(\kappa_1, \kappa_2, \kappa_3)$, we calculate the cut off w and estimate the concerned type I error rate taking n = 60 and 240 for ρ, τ and ρ^* allocation rules. Computed type I error rates show that the proposed allocation rule ρ controls the type I error better than its competitors (see Table 5).

We have explored so far the properties of the considered allocation designs for von Mises responses. But these allocation designs are developed without considering any specific distributions from the circular family and hence it is of interest to further investigate the properties for some other relevant response distribution. In particular, we consider wrapped Cauchy responses and provide a three dimensional plot of the limiting allocation proportion (LAP) to treatment 1 under the ρ rule. Specifically, assuming the response variable for treatment j as wrapped Cauchy with mean direction μ_j and concentration parameter $\xi_j \in (0, 1)$, we fix μ_1 at 5° and varying (μ_2, μ_3) we provide the plot for various combinations of (ξ_1, ξ_2, ξ_3) in Fig. 1. As expected the ethical norms are also maintained for the wrapped Cauchy responses as long as LAP is concerned.

4.4. Redesigning a real clinical trial: SICS trial

In order to judge the efficacy of the proposed allocation design in real situation, we consider a real clinical trial involving circular responses. A small incision cataract surgery (SICS) trial was conducted at the Disha Eye Hospital and Research Center, Barrackpore, West Bengal, India, over a period of two years (2008–10) (Bakshi, 2010). We take into account three competing treatments from the study, namely SICS with Snare technique (see Basti, Vasavada, Thomas, & Padhmanabhan, 1993), SICS with Irrigating Vectis technique (see Masket, 2004) and Torsional Phucoemalsification (see Mackool & Brint, 2004) with 19, 18 and 16 observations respectively. The response variable was 4 times the induced angle of astigmatism in modulo 2π system. Clearly the response is circular in nature and hence is appropriate to judge the performance of the proposed allocation. The responses to Snare, Irrigating Vectis and Torsional Phucoemalsification techniques are assumed to follow von Mises with parameters (μ_s, κ_s), (μ_v, κ_v) and (μ_t, κ_t), respectively (see Table 6).

For the Snare technique, parameters are estimated as $\hat{\mu}_s = 20.67°$, $\hat{\kappa}_s = 1.59$; for Irrigating vectis, these estimates are $\hat{\mu}_v = 52.71°$, $\hat{\kappa}_v = 1.27$; and for Torsional Phucoemalsification, the estimates of the parameters are $\hat{\mu}_t = 2.29°$, $\hat{\kappa}_t = 4.99$, respectively. Treating these estimated as the true parameter, we perform Watsons's goodness of fit test (Mardia & Jupp, 2004), findings of which satisfy the von Mises assumption. Then the Torsional Phucoemalsification appears to be much better than its competitors as the mean direction is closer to the preferred direction as well as has more concentration towards the preferred direction. The Snare's technique emerges as the second best treatment as far as the distance from the preferred direction with a competitively higher concentration is concerned.



(a) $\xi_1 = 0.5, \xi_2 = 0.5, \xi_3 = 0.5$

(b) $\xi_1 = 0.8, \xi_2 = 0.8, \xi_3 = 0.8$

(c) $\xi_1 = 0.5, \xi_2 = 0.8, \xi_3 = 0.8$

(d) $\xi_1 = 0.8, \xi_2 = 0.8, \xi_3 = 0.5$

Fig. 1. Limiting allocation proportions under Wrapped Cauchy responses.

Treating these parameter values as the true values we run a simulation with 10,000 iterations using ρ, τ and ρ^* rules with these 3 treatments taking $c = 30°$. We report the EAP values for different treatments together with the respective standard deviations (SD) in Table 5.

The results clearly indicate that the allocation rules ρ, τ and ρ^* successfully allocate larger number of study subjects to the better performing treatment arms as compared to the actual allocation, which assigned fewer number of subjects

Table 3
Comparison of power under general alternative.

$(\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3)$	Power							
	n = 60				n = 240			
	ρ	τ	$\rho^*(h = 0.6)$	Equal	ρ	τ	$\rho^*(h = 0.6)$	Equal
(5, 5, 5, 2, 2, 2)	0.05	0.05	0.05	0.05	0.05	0.05	0.05	0.05
(5, 10, 15, 2, 2, 2)	0.118	0.112	0.122	0.118	0.323	0.321	0.359	0.355
(5, 15, 25, 2, 2, 2)	0.319	0.312	0.328	0.324	0.814	0.811	0.842	0.855
(5, 30, 45, 2, 2, 2)	0.861	0.844	0.838	0.810	1.000	1.000	1.000	1.000
(5, 45, 60, 2, 2, 2)	0.990	0.992	0.962	0.976	1.000	1.000	1.000	1.000
(5, 75, 90, 2, 2, 2)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
(5, 5, 5, 1, 2, 2)	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
(5, 10, 15, 1, 2, 2)	0.070	0.080	0.070	0.070	0.090	0.070	0.150	0.060
(5, 30, 45, 1, 2, 2)	0.244	0.222	0.321	0.248	0.926	0.927	0.997	0.944
(5, 45, 60, 2, 2, 2)	0.663	0.650	0.688	0.664	1.000	1.000	1.000	1.000
(5, 75, 90, 2, 2, 2)	0.989	0.982	0.993	0.969	1.000	1.000	1.000	1.000
(5, 5, 5, 2, 2, 1)	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
(5, 15, 25, 2, 2, 1)	0.108	0.110	0.188	0.112	0.487	0.481	0.556	0.510
(5, 30, 45, 2, 2, 1)	0.379	0.349	0.446	0.269	0.970	0.971	0.991	0.982
(5, 45, 60, 2, 2, 1)	0.750	0.721	0.772	0.634	1.000	1.000	1.000	1.000
(5, 75, 90, 2, 2, 2)	0.992	0.994	0.988	0.991	1.000	1.000	1.000	1.000

Table 4
Comparison of power under directional alternative.

$(\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3)$	Power							
	n = 60				n = 240			
	ρ	τ	$\rho^*(h = 0.6)$	Equal	ρ	τ	$\rho^*(h = 0.6)$	Equal
(5,5,5,1,1,1)	0.050	0.050	0.053	0.050	0.050	0.050	0.050	0.050
(5,10,15,1,1,1)	0.100	0.080	0.062	0.070	0.321	0.319	0.339	0.355
(5,15,25,1,1,1)	0.160	0.150	0.069	0.170	0.810	0.811	0.819	0.862
(5,30,45,1,1,1)	0.210	0.200	0.180	0.240	0.919	0.910	0.900	0.920
(5,45,60,1,1,1)	0.490	0.455	0.420	0.460	1.000	1.000	1.000	1.000
(5,60,75,1,1,1)	0.760	0.780	0.721	0.770	1.000	1.000	1.000	1.000
(5,75,90,1,1,1)	0.850	0.840	0.788	0.865	1.000	1.000	1.000	1.000
(5,100,120,1,1,1)	0.922	0.915	0.889	0.940	1.000	1.000	1.000	1.000
(5,5,5,1,2,2)	0.050	0.050	0.050	0.050	0.050	0.050	0.050	0.050
(5,10,15,1,2,2)	0.060	0.070	0.089	0.090	0.090	0.070	0.090	0.080
(5,15,25,1,2,2)	0.315	0.305	0.331	0.340	0.620	0.600	0.622	0.640
(5,30,45,1,2,2)	0.695	0.695	0.668	0.670	0.926	0.927	0.889	0.944
(5,45,60,1,2,2)	0.855	0.865	0.834	0.840	1.000	1.000	1.000	1.000
(5,60,75,1,2,2)	0.921	0.900	0.902	0.930	1.000	1.000	1.000	1.000
(5,75,90,1,2,2)	0.956	0.955	0.937	0.960	1.000	1.000	1.000	1.000
(5,100,120,1,2,2)	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

Table 5
Type I error rates for T_n and W_n^* tests with n = 60.

$(\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3)$	Type I error rates		
	ρ	τ	$\rho^*(h = 0.6)$
(5,5,5,2,2,2)	0.080**[0.010]**	0.110**[0.120]**	0.120**[0.110]**
(5,5,5,1,2,2)	0.090**[0.120]**	0.130**[0.130]**	0.140**[0.150]**
(5,5,5,2,2,1)	0.100**[0.120]**	0.150**[0.150]**	0.140**[0.140]**

Boldface figures within [.] indicate the Type I error rates for the W_n^* test.

Table 6
Allocation to different treatment arms.

Treatment	EAP(SD)				
	ρ	τ	$\rho^*(h = .6)$	$\rho^*(h = .7)$	Actual
Snare	.289(0.07)	.331(0.07)	.370(0.12)	.422(.12)	.358
Irrigating Vectis	.187(0.08)	.238(0.08)	.341(0.13)	.383(.11)	.339
Torsional Phucoemalsification	.525(0.08)	.431(0.07)	.289(0.11)	.194(.11)	.301

to the better treatment (i.e. Torsional Phucoemalsification). However, as indicated earlier, the performance of the ρ^* rule is observed sensitive with the choice of h (see Table 6).

5. A treatment selection criterion

We have developed so far allocation designs for general class of circular responses, which are found to be effective for assigning larger number of subjects to promising treatment arms. Since in general, clinical trials involve human beings, it would be ethically more appealing if the inferior treatment arms are dropped as early as possible rather than continuing with all the treatments till the trial terminates. Motivated by the works of Bretz, Koenig, Brannath, Glimm, and Posch (2009) and Maurer, Branson, and Posch (2009), we suggest to run the trials in stages, where after the end of each stage the least performing treatment arm is dropped. Assuming that the response distribution for the j th treatment belongs to a circular family of distributions with mean direction μ_j and concentration $\kappa_j, j = 1, 2, ..t$, we describe the stage-wise treatment selection procedure below.

5.1. The proposed early stopping rules

Assume that the patients arrive sequentially one by one. At the first stage tn_0 patients are assigned among the t treatments using some allocation rule. At the end of the first stage, the maximum likelihood (ML) estimates of the parameters are computed from the first stage data consisting tn_0 observations and treatment k is dropped if $d(\mu_k^*, 0) > \max_{j\neq k}(d(\mu_j^*, 0))$, where μ_k^* is the maximum likelihood estimate of mean direction μ_k based on the available first stage data. As a treatment arm is dropped, from $(tn_0 + 1)$st sample onwards, patients are allocated among the remaining $(t - 1)$ treatment arms. Since the second stage incorporates less number of treatment arms, the number of patients in this stage can be kept fewer than that of the first stage. In fact, for all the upcoming stages, number of assignments can be set in a decreasing manner. For a typical stage s, we suggest to take assignments to be $n_0(t - s + 1)$.

Now to treat $n_0(t - 1)$second stage patients, the ML estimates of the parameters obtained from the first stage data are plugged into the allocation function and patients are assigned to treatments accordingly. However, unlike usual data dependent allocation designs, here the allocation probabilities are calculated for each stage and kept fixed throughout that stage. At the end of the second stage, the least performing treatment is dropped using the same criterion stated earlier.

To estimate the plug-in parameter for the third stage, instead of combining the first stage and second stage data, first stage and second stage estimates are combined suitably. For estimating the concentration parameters, simple average of stage-wise estimates is taken as the combined estimate. However, for the mean direction parameter, sample mean direction of the stage-wise estimates is taken as the combined estimate. Once the estimated values of the parameters are available, they are plugged into the same allocation function and $n_0(t - 2)$ patients are assigned in the third stage accordingly. Again at the end of the third stage, the worst performing treatment is dropped. The treatment dropping is continued in this fashion until a single treatment remains as the winner.

However, similar to the notions of sequential treatment selection design, we suggest that if there is enough evidence that all the treatment arms are equally effective, the trial should be terminated readily, without continuing up to the end. Similarly if there is enough evidence that one of the treatment arms is unanimously better over others, then also the trial should be terminated early. Consequently, we suggest two practical modifications of the proposed treatment selection design. The first alternative is based on the early stopping for efficacy. Here an interim analysis is performed in which treatments are allocated to each of the treatment arms according to some response adaptive allocation rule. Once the interim data is obtained, a test is performed using the multiple comparison test statistic $max(W_2, W_3)$. If the null hypothesis of homogeneity is rejected, treatment 1 is considered the winner (i.e. efficient) and the trial is terminated immediately. If the homogeneity hypothesis is not rejected, the trial continues as per the suggested treatment selection design. This selection procedure is termed early stopping rule for efficacy (ESFE).

The next alternative is based on the early stopping for futility. Here, based on the data of interim analysis if the null hypothesis of homogeneity is not rejected according to the multiple comparison test statistic $max(W_2, W_3)$, then no treatment is considered as winner and hence futility is achieved regarding the selection of best treatment arm. Thus it is suggested to terminate the trial without any further treatment allocation. If the homogeneity hypothesis is rejected after the interim analysis, then the trial is continued by virtue of treatment selection scheme described as before and no early stopping is recommended. This selection procedure is termed as early stopping rule for futility (ESFF).

5.2. Performance analysis of early stopping rules

Now we assess the performance of the proposed early stopping designs assuming von Mises responses. Here the total sample size is fixed at $n = 60$, that is, if there is no early stopping, at most 60 patients will be allocated to the treatment arms 1, 2 and 3. For the interim analysis, the sample size is set at n^* i.e. n^* patients are allocated to the treatment arms based on response adaptive schemes. In general, it is recommended to set the sample size of interim analysis atleast 50% of the total sample size, since smaller sample size for interim analysis, may lead to fallacious conclusion. On the other hand, if a larger sample size is set for the interim analysis, then early stopping rule almost coincides with the previously described fixed sample selection rule. So a compromise between the two scenarios is selected in this case. We have considered several values of n^* between 30 to 40 and the results obtained indicate similar conclusions. For the sake of illustration, we report the result, for $n^* = 40$ with the proposed ρ rule as the baseline allocation design. For the computation, the mean direction parameter of treatment 1 (i.e. μ_1) is kept at 5° which is nearest to the preferred direction

Table 7
Performance of the early stopping rules for von Mises responses with $n^* = 40$.

$(\mu_1, \mu_2, \mu_3, \kappa_1, \kappa_2, \kappa_3)$	Expected sample size						EP	
	ESFF			ESFE			ESFF	ESFE
	1	2	3	1	2	3		
(5, 5, 5, 2.0, 2.0, 2.0)	14.222	13.614	13.804	20.311	19.887	19.782	0.0352	0.6354
(5, 15, 25, 2.0, 2.0, 2.0)	17.055	15.757	13.168	22.556	20.634	16.230	0.0591	0.3455
(5, 45, 60, 2.0, 2.0, 2.0)	28.155	18.497	12.288	20.300	15.153	10.927	0.0055	0.0062
(5, 60, 75, 2.0, 2.0, 2.0)	31.638	17.051	10.991	18.777	12.924	9.719	0.0014	0.0008
(5, 75, 90, 2.0, 2.0, 2.0)	34.307	15.413	10.260	19.295	11.529	9.376	0.0002	0.0002
(5, 5, 5, 1.0, 2.0, 2.0)	11.773	14.885	14.982	14.409	22.815	22.736	0.0412	0.8621
(5, 15, 25, 1.0, 2.0, 2.0)	13.772	16.735	14.533	16.641	23.527	18.912	0.0782	0.5822
(5, 45, 60, 1.0, 2.0, 2.0)	22.819	20.344	13.717	17.098	18.590	13.112	0.0184	0.1152
(5, 60, 75, 1.0, 2.0, 2.0)	25.929	19.857	12.654	17.017	15.385	11.558	0.0422	0.0422
(5, 75, 90, 1.0, 2.0, 2.0)	29.246	18.378	11.836	17.438	13.503	10.479	0.0106	0.0164
(5, 5, 5, 2.0, 1.0, 1.0)	17.130	12.595	12.635	25.656	17.168	17.116	0.0312	0.4564
(5, 15, 25, 2.0, 1.0, 1.0)	17.829	12.858	12.193	26.949	17.196	15.755	0.0322	0.3223
(5, 45, 60, 2.0, 1.0, 1.0)	22.354	13.750	11.456	29.606	16.332	12.942	0.0051	0.0422
(5, 60, 75, 2.0, 1.0, 1.0)	26.184	13.686	11.350	29.718	15.493	11.889	0.0042	0.0102
(5, 75, 90, 2.0, 1.0, 1.0)	30.678	13.649	11.173	28.781	13.828	10.831	0.0032	0.0044

0° and mean directions for treatments 2 and 3 (i.e. μ_2 and μ_3) are varied keeping μ_1 least. So whenever the concentration parameter of treatment 1 (i.e. κ_1) is equal or greater than concentration parameters of treatments 2 and 3 (i.e. κ_2 and κ_3), treatment 1 can be considered as better over its competitors due to least value of mean direction. But if concentration of treatment 2 or treatment 3 is greater than that of treatment 1, then even for a lower value of mean direction, treatment 1 cannot be regarded as the best treatment. In Table 7, we have reported the expected allocated sample size to each of the treatment arms, along with the error probability (EP) of not selecting treatment 1 as the winner. We note that, when the mean directions are nearer to each other the ESFF rule successfully terminates the trial early with the total expected allocation to treatments about 40, which is the sample size pre specified for the interim analysis. An advantage of ESFF rule is that for treatments having no significant difference in mean directions, error probability varies around a low value, that is, the scheme successfully controls the possibility of selecting an inferior treatment as the best treatment. This happens due the fact that, for treatments having little or no difference, ESFF scheme ensures after the interim stage that no treatment would emerge as the winner. On the other hand, ESFE rule ensures sample size reduction for large treatment differences. Although both the selection rules give optimistic results, ESFF is ethically slightly better as far as controlling the selection of an inferior treatment is concerned. It can be added further that each of these rules, ethical imperative of skewing the subjects towards the better treatment arm is maintained.

5.3. Application to SICS trial

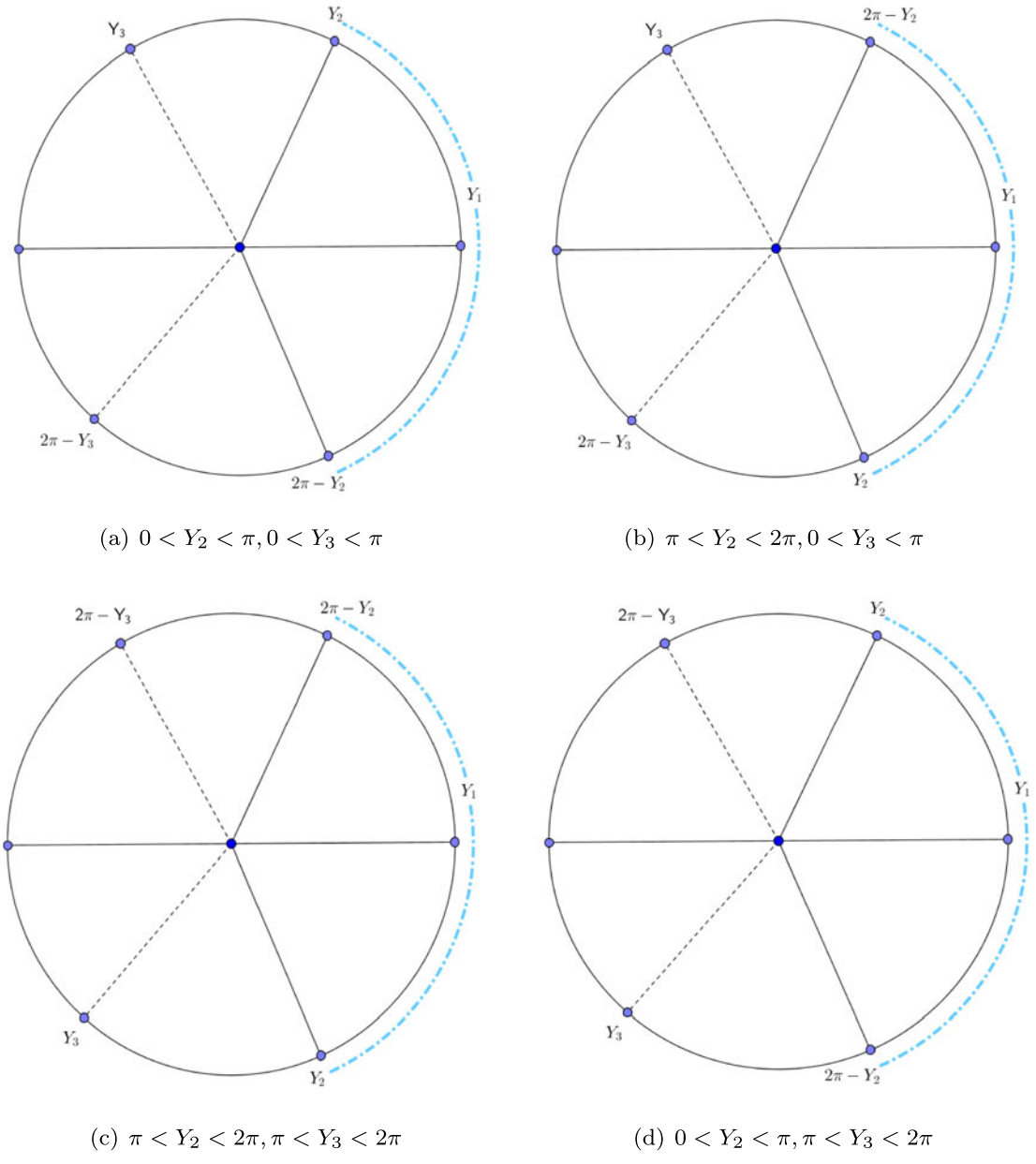
Once again the SICS trial is considered to analyse the effectiveness of the selection rule in the light of a real life data. The trial is redesigned through a simulation study with 10,000 repetitions of the proposed selection rule, where the parameter values are set as in Section 4.4. We consider $n_0 = 10$ for this exercise, that is, 30 samples are taken for the first stage, and the remaining 23 samples are kept for the second stage (total sample size is taken to be 53, which is the total sample size of the original data, combining three treatments; see Section 4.4). For SICS trial, the experiment does not terminate at first stage and the selection criterion results in 55.19% allocation towards Torsional Phucoemalsification. The estimated error probability is obtained as 0.00080, which indicates that the suggested selection criterion successfully detects Torsional Phucoemalsification as the best treatment for the SICS trial.

6. Concluding remarks

The current work develops a sensible response adaptive allocation design for multi-treatment clinical trials, where the patient responses are circular in nature. However, the most appealing aspect of the work is the development of a treatment selection procedure within the framework of a response-adaptive randomization. The objective behind any treatment selection procedure is to drop treatments with worse performance. Early identification of an ineffective treatment not only increases the acceptability of the trial but also increases the ethical impact. Encouraging findings make the proposed procedure attractive from a practitioner's viewpoint. However, in general, covariates are associated with the patients and the subsequent development incorporating covariate information is a topic for further research.

Acknowledgements

The authors sincerely thank the referees, Editor and the Associate Editor for their valuable suggestions, which led to an improvement over the earlier version.



(a) $0 < Y_2 < \pi, 0 < Y_3 < \pi$ (b) $\pi < Y_2 < 2\pi, 0 < Y_3 < \pi$

(c) $\pi < Y_2 < 2\pi, \pi < Y_3 < 2\pi$ (d) $0 < Y_2 < \pi, \pi < Y_3 < 2\pi$

Fig. 2. Feasible region for $\{(Y_1, Y_2, Y_3) : d(Y_1, 0) < d(Y_2, 0) < d(Y_3, 0)\}$.

Appendix

Proof of the Lemma. Assume t = 3, then ρ_1 is the sum of probabilities of disjoint events $d(Y_1, 0) < d(Y_2, 0) < d(Y_3, 0)$ and $d(Y_1, 0) < d(Y_3, 0) < d(Y_2, 0)$. The feasible region for the former event with different choices of (Y_1, Y_2, Y_3) is sketched in Fig. 2. Interchanging Y_2 and Y_3, the other events can be visualized.

Now for general t, we note that the event $d(Y_k, 0) < \min_{1 \le j(\ne k) \le t} d(Y_j, 0)$ is equivalent to $d(Y_k, 0) < d(Y_j, 0)$ for all $j \ne k$. Then from Fig. 2, we find that $d(Y_k, 0) < d(Y_j, 0)$ holds if and only if either $(0 < Y_k < \pi, Y_k < Y_j < 2\pi - Y_k)$ or $(\pi < Y_k < 2\pi, 2\pi - Y_k < Y_j < Y_k)$ hold and hence the lemma follows. □

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