JOURNAL OF STATISTICAL THEORY AND PRACTICE
2017, VOL. 11, NO. 4, 719–730
http://dx.doi.org/10.1080/15598608.2017.1307147

An adaptive allocation design for circular treatment outcome

Atanu Biswas[a], Rahul Bhattacharya[b], and Taranga Mukherjee[b]

[a]Applied Statistics Unit, Indian Statistical Institute, Kolkata, India; [b]Department of Statistics, University of Calcutta, Kolkata, India

ABSTRACT
A number of allocation designs are developed for continuous and binary treatment outcomes to assign a higher number of subjects to the treatment doing better in course of the trial. However, if the response is circular in nature, the definition of a better treatment differs from that under the linear response and hence the already developed designs lack appropriateness. In the current work, redefining the notions of superiority, we develop an allocation function in the context of circular treatment outcomes. Using a response-adaptive route for practical implementation, we study the resulting design both theoretically and numerically and finally illustrate the performance for a real-life example on cataract surgery.

ARTICLE HISTORY
Received 27 September 2016
Accepted 12 March 2017

KEYWORDS
Adaptive allocation; circular responses; von Mises distribution

AMS SUBJECT CLASSIFICATION
62L05

1. Introduction

A clinical trial is run to determine the efficacy of the competing treatments based on the response of the participating patients. However, involvement of human beings in such trials necessitates keeping certain ethical norms, and hence, providing the best possible care for individual patients is required. Since the treatments under study vary in effectiveness, assigning a larger fraction of subjects to the better performing treatment is a suitable option to keep ethical norms. Thus, a skewed allocation is required instead of the age-old practice of blindly favoring each treatment. However, the best treatment is not known to the experimenter in advance and relying on the accrued data to decide further allocations becomes the only option. Clearly, a response-adaptive procedure with the ability to assign every subject based on the data available so far is consistent with the requirement.

The key element of a response-adaptive procedure is an allocation function, a function of the response distribution and the associated parameters. Sequentially updated estimates of the allocation function are used to assign incoming subjects. The allocation function is chosen to ensure skewing toward the better performing treatment. A number of such allocation designs can be found in the literature for both discrete and continuous treatment outcomes. We refer interested readers to the review works of Biswas (2001), Biswas and Bhattacharya (2016), and Sverdlov (2016) and book-length treatments of Atkinson and Biswas (2014) and Rosenberger and Lachin (2016) for an exposure to the different perspectives of allocation designs. Some real-life applications of the response adaptive randomization are also found in Bartlett et al. (1985), Tamura et al. (1994), and Biswas and Dewanji (2004).

CONTACT Rahul Bhattacharya rahul_bhattya@yahoo.com Department of Statistics, University of Calcutta, 35, Ballygunge Circular Road, Kolkata 700 019, India.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/ujsp.

A circular response refers to the responses indicated by angles and hence measured in radians or degrees (Mardia and Jupp 2000). In biomedical studies, circular data often arise in the context of ophthalmology or orthopaedics. The responses obtained from rotation of joints (shoulder, waist, or knee) and eyeball movements are standard examples of circular responses in practice. Formally, a circular random variable, Θ, is a random point on the circumference of a circle with unit radius. For any realization θ, angles θ and $\theta + 2p\pi$ where $p = 0, \pm 1, \pm 2, ..,$ correspond to the same point on the unit circle and hence we get an observation on the whole real line. Consequently, the distribution function F of a circular random variable Θ is defined by

$$F(\theta) = P(0 < \Theta \leq \theta), 0 \leq \theta \leq 2\pi.$$

However, due to periodicity of Θ, any arc of length 2π on the unit circle has probability 1 (Mardia and Jupp 2000), and hence we get the additional restriction

$$F(\theta + 2\pi) - F(\theta) = 1, -\infty < \theta < \infty.$$

Since the starting point coincides with the end, there is no natural ordering of the observations. For example, unlike linear responses, an angle of 350 degrees is not too far from the origin (i.e., 0 degrees or 360 degrees). Consequently, adoption of a usual convention "higher is favorable" or "lower is favorable" leads to fallacious interpretations (Mardia and Jupp 2000). To circumvent this problem, the circular responses are compared with each other with respect to a reference point, called the preferred direction. The choice of preferred direction can be data driven, or this can be preselected as per the practitioner's choice. In the field of medical research the preferred direction is usually set according to the desired medical condition. For example, for studies related to shoulder movement, it is usually seen that a perfect shoulder allows 90 degrees of internal rotation (Jain et al. 2013) and hence the preferred direction is set at 90 degrees. For a two-treatment clinical trial, an allocation design is developed in Biswas et al. (2015) under circular responses, where the central idea was motivated by a real-life small-incision cataract surgery (SICS) trial. However, the authors considered the family of von Mises responses exclusively.

In the current work, we suggest an allocation function for a general class of circular responses and study the related properties. The allocation function together with relevant properties is discussed in section 2. In section 3, we provide an assessment of the performance of the proposed allocation for widely used response distributions. We also use the proposed allocation to redesign some real clinical trial in section 4 and conclude with a discussion of related issues in section 5.

2. The allocation design

2.1. *Relative effectiveness measure for circular responses*

Consider a clinical trial involving two treatments A and B. The potential outcome Y_k for a subject assigned to treatment k is assumed circular in nature (i.e., measured in radians or degrees). We, therefore, assume that the distribution of Y_k belongs to some circular family of distributions (Mardia and Jupp 2000). For linear responses, if a lower response indicates

a favorable situation, the treatment producing frequent lower responses over its competitors is considered as most promising. Naturally, one can use the quantity $P(Y_A < Y_B)$ to measure the relative effectiveness of treatment A (Bandyopadhyay and Bhattacharya 2016). But circular responses are periodic in nature and hence binary operations for linear responses are no longer applicable. Therefore, we need to develop analogous definitions of a promising treatment and a relative effectiveness measure.

Suppose the preferred direction for the trial is known to be μ_0; then a response close to μ_0 is considered favorable. However, circular responses are angles and the distance between the response and the preferred direction is not just their numerical difference. Therefore, we consider one of the formulations by Jammalamadaka and SenGupta (2001) and take the smaller arc length between the points along the circumference to define the circular distance between to angles. Specifically, we use the quantity $d(\psi, \theta) = \min(\psi - \theta, 2\pi - (\psi - \theta))$ to measure the distance between two arbitrary angles ψ and θ. Since $d(\psi, \theta)$ is a linear quantity, we can apply linear statistical methods on such distance measures. Then treatment A is the most promising if the corresponding distance measure $d(Y_A, \mu_0)$ is lower than that corresponding to treatment B. Therefore, under circular response models, response Y_A is more promising than Y_B, denoted by $Y_A \overset{C}{>} Y_B$, if and only if the inequality $d(Y_A, \mu_0) < d(Y_B, \mu_0)$ holds. Consequently the relative effectiveness of treatment A can be measured by $\rho_A = P\{d(Y_A, \mu_0) < d(Y_B, \mu_0)\}$, which is nothing but the the probability that treatment A is superior to treatment B. Naturally, for equally promising treatments $\rho_A = \frac{1}{2}$ and $\rho_A > \frac{1}{2}$, if treatment A is more promising.

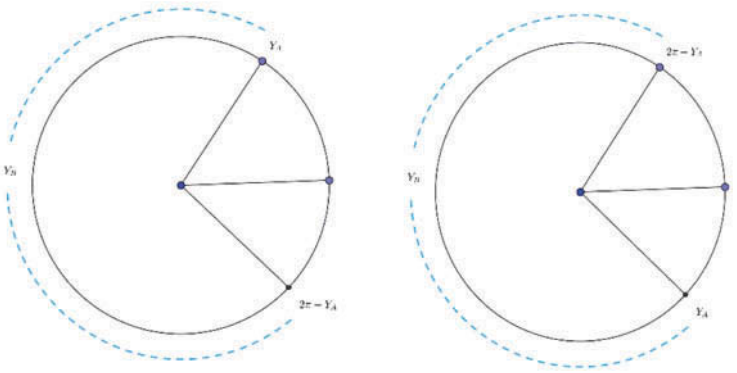
2.2. *The allocation function*

In any clinical trial, the ethical goal is to skew the allocation toward the better performing treatment, and consequently, we need a function to accomplish the goal. The preceding discussion suggests using ρ_A for the development of an allocation procedure with circular treatment responses. The relative effectiveness measure, as defined in the preceding, is an analogue of the allocation function developed by Bandyopadhyay and Biswas (2001) with entirely different notions. However, for further development, without loss of generality we take $\mu_0 = 0$. Then a quadrant-wise examination reveals that for $0 < Y_A < \pi$, $d(Y_A, 0) < d(Y_B, 0)$ reduces to $Y_A < Y_B < 2\pi - Y_A$, whereas for $\pi < Y_A < 2\pi$, the inequality simplifies to $2\pi - Y_A < Y_B < Y_A$. Therefore, $Y_A \overset{C}{>} Y_B$ holds if and only if $(0 < Y_A < \pi, Y_A < Y_B < 2\pi - Y_A)$ or $(\pi < Y_A < 2\pi, 2\pi - Y_A < Y_B < Y_A)$ is satisfied. The dotted arc outside the circle in Figure 1 indicates the portion described by the relation $Y_A \overset{C}{>} Y_B$.

If F_k is the distribution function of Y_k with f_k as the corresponding density, then we get the following expression:

$$\rho_A = \int_0^{\pi} \{F_B(2\pi - y) - F_B(y)\} f_A(y) dy + \int_{\pi}^{2\pi} \{F_B(y) - F_B(2\pi - y)\} f_A(y) dy.$$

Interestingly, if we consider another popular choice of distance measure, $d^*(\psi, \theta) = 1 - \cos(\psi - \theta)$, the region described by the inequality $d^*(Y_A, 0) < d^*(Y_B, 0)$ remains the same as that by the relation $d(Y_A, 0) < d(Y_B, 0)$. Hence the quantity ρ_A remains



(a) $0 < Y_A < \pi$ (b) $\pi < Y_A < 2\pi$

Figure 1. The region for $Y_A \overset{C}{>} Y_B$ given Y_A as the dotted arc.

invariant under the choice of distance measure. Moreover,the allocation function is derived for a general circular response distribution and hence can be implemented in practice for any class of circular response distributions. However, if the preferred direction is other than 0, one can either transform (Mardia and Jupp 2000), the data to make the preferred direction 0 radian (or degrees) or derive a similar expression of the concerned allocation function for the purpose.

2.3. *Implementing the allocation in practice*

The allocation functions (i.e., ρ_A), defined earlier, can be used to assign the subjects according to the degree of effectiveness of treatments whenever the response distribution becomes completely known to the experimenter. However, the distribution is never completely known, and we need to use appropriate estimates to run the allocation process. Specifically, if we assume that the response distributions have a common support and θ_k is the $d(\geq 1)$ component vector of parameters associated with the response distribution of treatment k, then $\rho_k = \rho_k(\theta_A, \theta_B)$, the allocation function for treatment k, becomes a function of the unknown parameters. Since data become available only with the progress of the trial, it would be reasonable to use sequentially updated estimates of the allocation function to set the allocation probability of an entering subject. The methodology is, therefore, consistent with the response adaptive philosophy of randomization (Atkinson and Biswas 2014).

In practice, n_0 subjects are initially assigned to each treatment arm to get the initial estimates and to start the response adaptive randomization from the $(2n_0 + 1)$th entering subject. If the allocation indicator of the ith entering subject is denoted by $\delta_{k,i}$ (i.e., $\delta_{k,i} = 1$ if the subject is assigned to treatment k and 0 otherwise), Y_{ki} is the corresponding potential response if treatment k is given to the subject, and $\mathcal{F}_j$ is the totality of information contained in the first j allocation and responses, then a response-adaptive randomization procedure can be defined by

$$P(\delta_{k,i+1} = 1|\mathcal{F}_i) = \rho_k(\widehat{\boldsymbol{\theta}}_{Ai}, \widehat{\boldsymbol{\theta}}_{Bi}), i \geq 2n_0,$$

where $\rho_k(\widehat{\boldsymbol{\theta}}_{Ai}, \widehat{\boldsymbol{\theta}}_{Bi})$ is a reasonable estimate of ρ_k based on the data available prior to the entry of the $(i+1)$th subject.

In practice, maximum likelihood estimates of θ_k are plugged in the expression of ρ_k to get the desired allocation probability at each stage. The maximum likelihood estimate of $\boldsymbol{\theta}_k$ at stage $i+1$ is, in general, the solution of the equations $\frac{\partial \mathcal{L}_i}{\partial \boldsymbol{\theta}_k} = \mathbf{0}$, where

$$\mathcal{L}_i = \mathcal{L}_i(\boldsymbol{\theta}_A, \boldsymbol{\theta}_B) = \prod_{j=1}^{i} \prod_{k=A,B} \{f_k(Y_{kj}, \boldsymbol{\theta}_k)\}^{\delta_{k,j}}$$

is the likelihood of the data based on the response and allocation history of i responses.

Suppose $N_{kn} = \sum_{j=1}^{n} \delta_{k,j}$ denotes the observed number of allocations to treatment k out of n assignments following the proposed response adaptive randomization. If the continuity of $\rho_k = \rho_k(\boldsymbol{\theta}_A, \boldsymbol{\theta}_B)$ in each of its arguments is assumed, then the proposed allocation function is achieved in the limit (for details see Hu and Zhang [2004]). Thus, we have the following result:

As $n \to \infty$,

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

almost surely for each $k = A, B$.

3. Evaluating the performance

3.1. *Performance measures and the response distribution*

For the assessment of the randomization procedure, we need to consider suitable response distributions together with appropriate performance measures. The evaluation of any response adaptive procedure has two major aspects, namely, ethics and efficiency. The observed proportion of subjects assigned to different treatments serves as a measure of ethics. The better the effectiveness of the treatment, the higher is the corresponding proportion. However, skewing the allocation toward the better performing treatment is not the only objective in a clinical trial, and in addition, detection of a small deviation in treatment effectiveness with high probability, that is, preserving a higher level of statistical power for a relevant hypothesis of equality of treatment effects, is also required. Thus, we calculate the following measures to investigate the performance in small samples:

- The distribution of incoming subjects to different treatments measured by the expected values of $\frac{N_{kn}}{n}, k = A, B$.
- The power of a relevant test of equality of treatment effects.

However, for the investigation of performance, we further require a specific assumption regarding the response distribution. We, therefore, assume that the response distribution for treatment j has a von Mises distribution (Mardia and Jupp 2000) with mean direction μ_j and concentration parameter κ_j with density function

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

where $0 < y \leq 2\pi$, $0 < \mu_j \leq 2\pi$, $\kappa_j > 0$, 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 $p \geq 0$.

Now under a response-adaptive setup with n assignments following the proposed allocation design, maximum likelihood estimators $\widehat{\mu}_j$ and $\widehat{k}_j$ are the unique solutions of $\tan(\widehat{\mu}_j) = \frac{\bar{S}_j}{\bar{C}_j}$ and $A(\widehat{\kappa}_j, 0) = (\bar{C}_j^{\,2} + \bar{S}_j^{\,2})^{1/2}$, respectively, where $\bar{C}_j = \frac{1}{N_{jn}}\sum_{i=1}^{n} \delta_{j,i}\cos(Y_{ji})$ and $\bar{S}_j = \frac{1}{N_{jn}}\sum_{i=1}^{n} \delta_{j,i}\sin(Y_{ji})$, $j = A, B$, and $A(\kappa, s) = I_{s+1}(\kappa)/I_s(\kappa), s = 0, 1, \ldots$. Plugging these estimates into the suggested allocation function, the allocation probability for the $(n + 1)$th subject is determined.

Following any allocation, the natural question is to carry out an inferential procedure for possible determination of the effective treatment. Since $\cos(\mu_A) > \cos(\mu_B)$ is indicative of the fact that treatment A performs better, a hypothesis of equality of treatment effects can be set as $H_0 : \cos(\mu_A) = \cos(\mu_B)$. For our purpose, we consider the test developed in Biswas et al. (2016) under $\kappa_A \neq \kappa_B$. The test is based on the statistic

$$W = \frac{T_A^2}{S_A^2} + \frac{T_B^2}{S_B^2} - \left(\frac{T_A}{S_A^2} + \frac{T_B}{S_B^2}\right)^2 \Big/ \left(\frac{1}{S_A^2} + \frac{1}{S_B^2}\right),$$

where

$$T_j = \arccos\frac{\bar{C}_j}{\sqrt{\bar{C}_j^2 + \bar{S}_j^2}} \text{ and } S_j^2 = \frac{1 - A(\widehat{\kappa}_j, 1)}{2N_{jn}A(\widehat{\kappa}_j, 0)}.$$

Larger values of W indicate deviation from the null hypothesis, and hence we reject H_0 if the observed value of W is too large.

3.2. *Simulation study*

To study the performance of the proposed allocation in small samples, we conduct a simulation study with 10,000 repetitions for different values of the parameters and n and report the expected allocation proportion to treatment A, denoted by EAP_A, along with the corresponding standard deviation, indicated by SD. We also report the power of the already-mentioned test at the 5% level of significance. These measures are also computed for complete randomization (CR), where each treatment is assigned with equal probability and hence a balance in the treatment allocation is expected. Obviously the ethical perspective is violated in CR but the power of a relevant test is expected to be higher. Thus, a comparison with CR is necessary to reveal how much better a skewed allocation rule performs in terms of power in addition to ethics. Fixing μ_A suitably, we choose μ_B in such a way that $\Delta = d(\mu_B, 0) - d(\mu_A, 0) > 0$ is satisfied. That is, the entire simulation is

conducted considering treatment A as the most promising. If μ_A and μ_B are both varying in the first two quadrants, $\Delta = \mu_B - \mu_A$. On the other hand, if μ_A is fixed in the first or third quadrant and μ_B lies in the third quadrant, Δ reduces to $2\pi - (\mu_B + \mu_A)$, and hence, in such a situation, treatment A is superior when $\mu_A < 2\pi - \mu_B$. However, if we fix μ_A in the third or fourth quadrant, then $\mu_A > \mu_B$ ensures the superiority of treatment A. The measures are calculated for various combinations of (μ_A, μ_B) addressing $\kappa_A = \kappa_B$, $\kappa_A > \kappa_B$ and $\kappa_A < \kappa_B$ separately and are provided in Table 1.

Since the allocation design is developed for a general class of circular response distributions, we further consider the wrapped Cauchy responses having the density function

$$f_j(y) = \frac{1}{2\pi} \frac{1 - \kappa_j^2}{1 + \kappa_j^2 - 2\kappa_j \cos(y - \mu_j)}$$

for response from the jth treatment, where $0 < y \leq 2\pi$, $0 < \mu_j \leq 2\pi$, and $0 < \kappa_j < 1, j = A, B$. It is worth mentioning that the mean direction for the above family is μ_j and κ_j is the concentration parameter. However, we provide only the plots (see Figure 3, shown later) of limiting allocation proportion (LAP) to the better treatment (i.e. treatment A) for

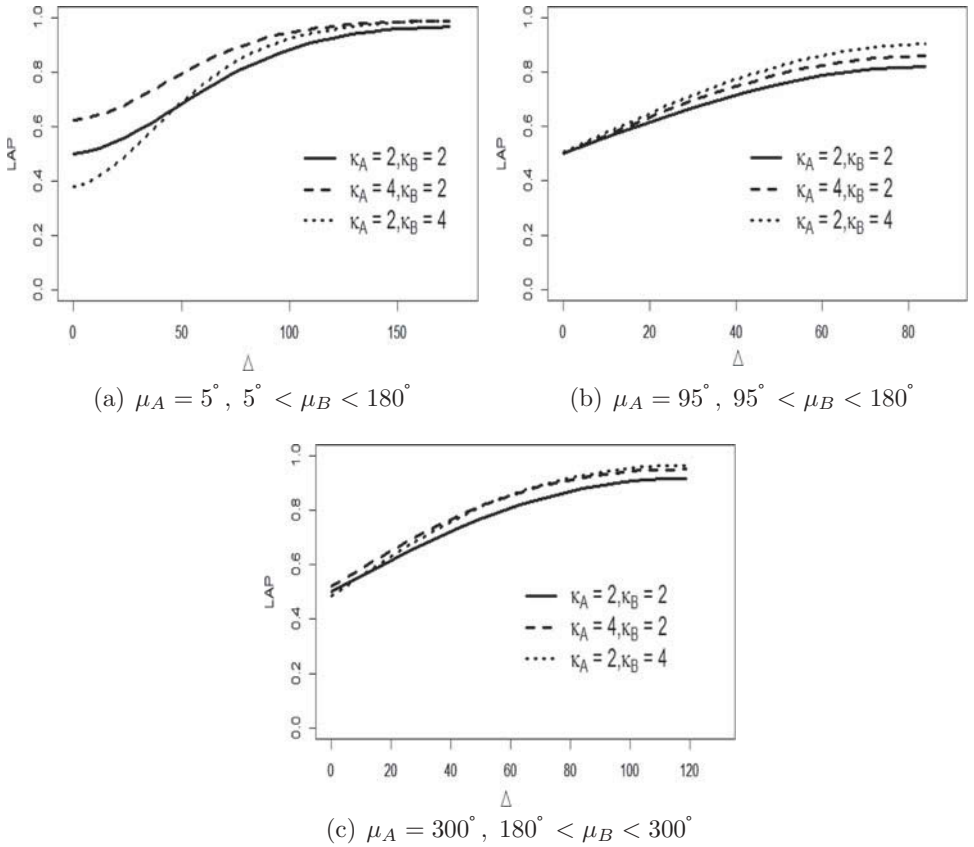
Table 1. Performance comparison for von Mises responses with $n = 40, 80$.

	$EAP_A(SD)$		Power	
$(\mu_A, \mu_B, \kappa_A, \kappa_B)$	n = 80	n = 40	n = 80	n = 40
(5,5,1,1)	.500 (0.08)	.500 (0.12)	0.050 [0.050]	0.050 [0.050]
(5,30,1,1)	.526 (0.08)	.525 (0.11)	0.332 [0.346]	0.148 [0.148]
(5,60,1,1)	.594 (0.08)	.588 (0.11)	0.849 [0.870]	0.472 [0.490]
(45,90,1,1)	.626 (0.08)	.617 (0.11)	0.577 [0.640]	0.292 [0.303]
(45,135,1,1)	.737 (0.09)	.720 (0.10)	0.858 [0.961]	0.605 [0.677]
(45,180,1,1)	.768 (0.07)	.753 (0.09)	0.920 [0.999]	0.751 [0.816]
(145,145,1,1)	.500 (0.07)	.500 (0.10)	0.050 [0.050]	0.050 [0.050]
(145,175,1,1)	.534 (0.07)	.526 (0.11)	0.195 [0.188]	0.102 [0.114]
(145,185,1,1)	.538 (0.07)	.529 (0.10)	0.196 [0.199]	0.106 [0.112]
(355,330,1,1)	.524 (0.08)	.525 (0.11)	0.336 [0.349]	0.146 [0.148]
(5,5,2,1)	.609 (0.07)	.601 (0.11)	0.050 [0.050]	0.050 [0.050]
(5,10,2,1)	.614 (0.08)	.608 (0.11)	0.080 [0.080]	0.060 [0.060]
(5,20,2,1)	.621 (0.07)	.615 (0.11)	0.200 [0.231]	0.120 [0.136]
(5,30,2,1)	.636 (0.07)	.629 (0.10)	0.392 [0.472]	0.224 [0.261]
(5,45,2,1)	.672 (0.07)	.653 (0.11)	0.592 [0.810]	0.427 [0.499]
(45,90,2,1)	.688 (0.06)	.681 (0.11)	0.514 [0.751]	0.342 [0.445]
(45,135,2,1)	.778 (0.07)	.761 (0.10)	0.965 [0.991]	0.636 [0.809]
(145,145,2,1)	.411 (0.07)	.403 (0.12)	0.050 [0.050]	0.050 [0.050]
(145,175,2,1)	.463 (0.06)	.454 (0.10)	0.280 [0.281]	0.118 [0.122]
(145,185,2,1)	.464 (0.06)	.455 (0.10)	0.280 [0.281]	0.116 [0.124]
(355,330,2,1)	.638 (0.07)	.626 (0.10)	0.400 [0.474]	0.224 [0.262]
(5,5,1,2)	.388 (0.07)	.395 (0.12)	0.050 [0.050]	0.050 [0.050]
(5,20,1,2)	.415 (0.07)	.419 (0.11)	0.107 [0.112]	0.060 [0.070]
(5,60,1,2)	.569 (0.07)	.561 (0.11)	0.902 [0.910]	0.651 [0.627]
(5,75,1,2)	.633 (0.07)	.625 (0.11)	0.968 [0.988]	0.822 [0.761]
(45,90,1,2)	.634 (0.07)	.634 (0.11)	0.858 [0.872]	0.492 [0.448]
(45,135,1,2)	.774 (0.06)	.759 (0.11)	0.996 [0.991]	0.883 [0.852]
(145,145,1,2)	.613 (0.08)	.602 (0.12)	0.050 [0.050]	0.050 [0.050]
(145,175,1,2)	.642 (0.06)	.626 (0.09)	0.359 [0.368]	0.184 [0.192]
(145,185,1,2)	.644 (0.06)	.624 (0.09)	0.361 [0.369]	0.184 [0.194]
(355,300,1,2)	.569 (0.07)	.561 (0.11)	0.902 [0.910]	0.651 [0.627]

Note. All the figures (except power) are expressed in degrees. Figures within the square brackets indicate the power for CR. EAP values for the CR are always 0.500 with SD around .04.

different combinations of the parameters. For the plot, we set $\mu_A = 5^\circ$ and vary μ_B in the first two quadrants, ensuring superiority of treatment A considering different combinations of (κ_A, κ_B).

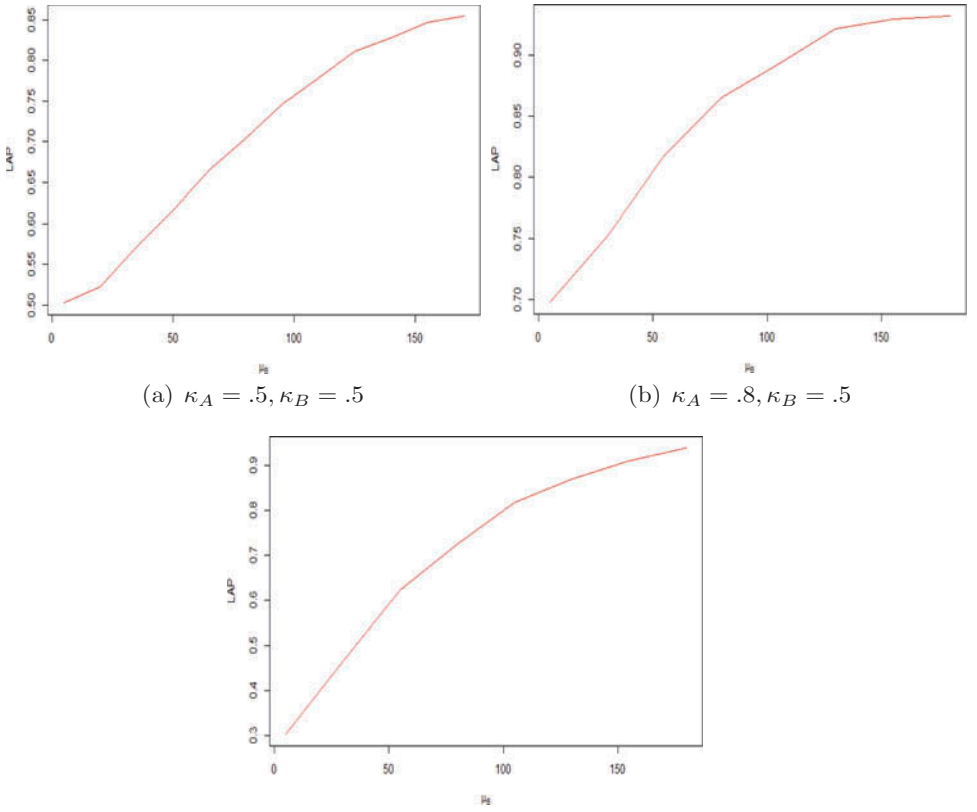
Remark 3.2.1. *From Table 1, we find that for $\kappa_A \geq \kappa_B$, EAP is at least 50% to the superior treatment (i.e., treatment A) and increases with the increasing superiority of treatment A. On the other hand, for $\kappa_A < \kappa_B$, the only exception is that EAP starts from a value less than 50% under the equality of treatment effects but increases steadily and crosses the 50% mark as the superiority of treatment A increases. However, if we compare the EAP to the superior treatment for different choices of (κ_A, κ_B), the highest EAP is observed when a higher concentration is attached with the superior treatment. An interesting feature of the EAP figures is that the skewing magnitude depends on the relative position of the arc (μ_A, μ_B) on the unit circle from the preferred direction (i.e., 0 degrees). For example, consider the EAP values corresponding to the combinations $(\mu_A = 5^\circ, \mu_B = 60^\circ, \kappa_A = \kappa_B = 1)$ and $(\mu_A = 45^\circ, \mu_B = 90^\circ, \kappa_A = \kappa_B = 1)$, that is, .594 and .626, respectively. Thus, higher skewing is observed for lower $\mu_B - \mu_A$. In further simulations, it is observed that an equal difference between mean directions does not ensure an equal amount of skewing. The magnitude of skewing depends on the position of the arc connecting the mean directions. However, equal arc lengths, equidistant from the preferred direction on either*



(a) $\mu_A = 5^\circ,\ 5^\circ < \mu_B < 180^\circ$ (b) $\mu_A = 95^\circ,\ 95^\circ < \mu_B < 180^\circ$

(c) $\mu_A = 300^\circ,\ 180^\circ < \mu_B < 300^\circ$

Figure 2. The limiting allocation proportion of treatment A under von Mises distribution



(a) $\kappa_A = .5, \kappa_B = .5$ (b) $\kappa_A = .8, \kappa_B = .5$

(c) $\kappa_A = .5, \kappa_B = .8$

Figure 3. Limiting allocation proportions (LAP) for wrapped Cauchy responses

side, provide an equal amount of skewing for equal concentrations. For further investigation of the effect of concentration parameters, we have provided a plot (Figure 2) of the limiting allocation proportion (LAP) to treatment A for varying choices of concentration parameters. The plot depicts the same story as told by the Table 1 figures, that is, strong impact of the concentration parameters on the allocation proportions. The same is observed when the response distribution is wrapped Cauchy (Figure 3).

Now we are in a position to evaluate the effect of different parameters on the power figures. Apart from minor fluctuations, a loss in power is observed as compared to the equal allocation. As expected, the higher the magnitude of EAP, more is the deviation from a balanced allocation and hence the higher is the loss. In particular, EAP values are higher for the configuration $\kappa_A \geq \kappa_B$ and hence the loss is significant. The reverse scenario is observed for $\kappa_A < \kappa_B$. Thus, the present allocation design not only allocates a larger number of subjects to the better performing treatment arm but also maintains more or less a similar precision level to CR. Hence the proposed allocation has the ability to control the trade-off between ethics and statistical precision (i.e., power) for a general class of circular response distributions.

4. Redesigning real clinical trial: SICS data

With an aim to judge the performance of the proposed allocation design in a real situation, we consider the real trial with astigmatic eyes conducted at the Disha Eye Hospital and Research Center, Barrackpore, West Bengal, India, over a period of 2 years (2008–2010) (Bakshi 2010). The study was a randomized trial with 37 astigmatic eyes. Astigmatism is an optical defect causing blurred vision. In the trial, out of the 37 patients for small-incision cataract surgery (SICS), the snare technique was applied on 19 patients and the irrigating vectis technique was applied on the remaining 18 patients. The response variable is obtained by multiplying 4 by the induced angle of astigmatism in modulo 2π system, and it is represented through separate rose diagrams for each treatment (i.e., snare and irrigating vectis techniques). Naturally, the response is circular in nature and hence is appropriate to judge the performance of the proposed allocation. Details of the trial and necessary information can be found in Biswas et al. (2015; 2016).

We start with the assumption that the responses to the snare technique (Treatment S) and irrigating vectis (Treatment V) are both distributed as von Mises distribution with parameters (μ_S, κ_S) and (μ_V, κ_V), respectively. However, for the justification of the validity of the assumed distribution for the data, we start with separate probability–probability (P-P) plots, which plot empirical distribution function for each data point against the corresponding value of the distribution function for the assumed distribution. Naturally, a fit is judged to be good if the plotted points are scattered close to the diagonal line connecting the origin with the point (1,1). The estimates of the unknown parameters assuming von Mises distribution are obtained from the data as $\hat{\mu}_S = 17.57^\circ$, $\hat{\kappa}_S = 1.478$, $\hat{\mu}_V = 32.04^\circ$ and $\hat{\kappa}_V = 1.504$. Assuming these values as the true parameters, we construct P-P plots for each treatment and provide them in Figure 4. The plot reveals the appropriateness of the Von Mises assumption. Watson's test (Jammalamadaka and SenGupta 2001), an equivalent to a goodness-of-fit test for circular responses, also supports the preceding distributional assumption. Now treating the estimates of the parameters as the true parameter values, we redesign the SICS trial using the proposed allocation procedure with trial size $n = 37$. For our purpose, we assume that the responses are immediate, that is, that there are no delays or staggered entries. We carry out the allocation using the

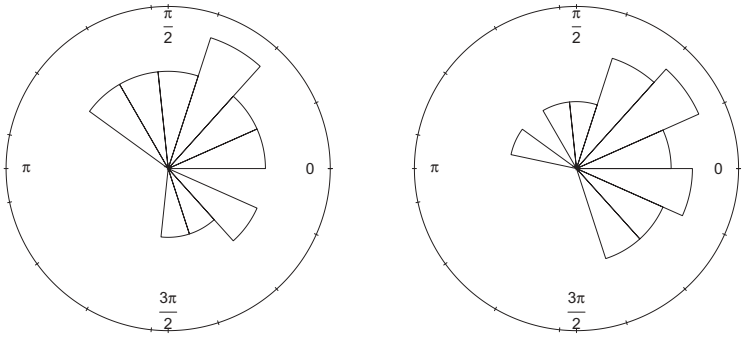


Figure 4. Rose diagram for the angle of astigmatism. (a) Responses from irrigating vectis. (b) Responses from snare technique.

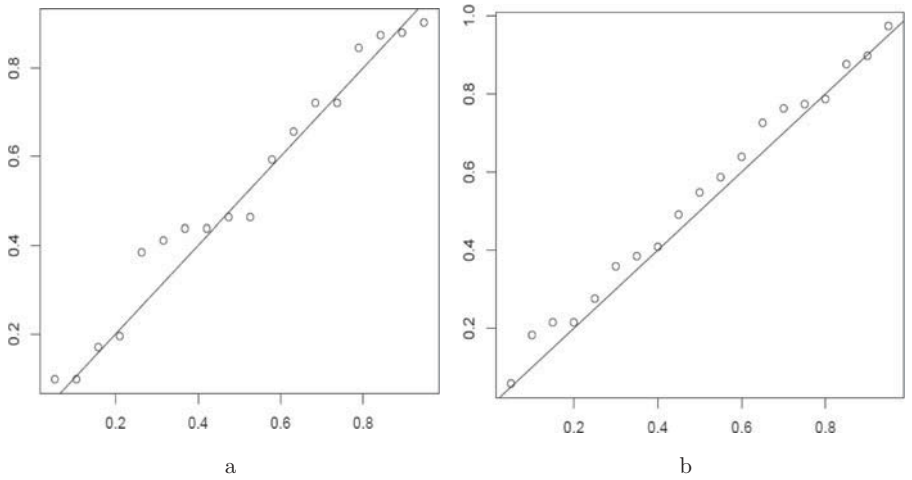


Figure 5. P-P plot to assess von Mises responses; (a) irrigating vectis; (b) snare.

proposed allocation design and repeat the procedure 10,000 times. The redesigning results in assigning 53.79% (i.e., 20 in number) subjects to the snare technique with a standard error of 10%. However, the original trial adopted a balanced procedure to assign 37 patients to the two treatments and concluded with the marginal superiority of the snare technique. The redesigning using the proposed response adaptive methodology supports the same feature but with a slightly higher number of assignments to the better treatment, as there is no overwhelming superiority of either treatment over the other.

In addition, we investigate the consequences, when the responses are assumed to have wrapped Cauchy distribution (see section 3.2). As done earlier, we assume the response parameters (μ_S, κ_S) and (μ_V, κ_V) for treatments S and V, respectively and obtain the corresponding estimates $\hat{\mu}_S = 24.07^0, \hat{\kappa}_S = 0.5073,$ and $\hat{\mu}_V = 63.84^0, \hat{\kappa}_V = 0.5078.$ Redesigning under the said response model results in 63% allocation to the snare treatment with a standard error of 8%. Thus under the wrapped Cauchy responses, an excess of about 10% subjects are expected to receive the better treatment. However, these results are obtained under a misspecified model and therefore the results are not significant, except for the fact that the proposed allocation design has the ability to assign subjects according to the treatment superiority.

Thus, in general, the proposed allocation not only favors the better treatment for more allocation but also shows sensitivity to moderately small difference in effectiveness and hence can be adopted in trials where the outcome is circular in nature.

5. Concluding remarks

This work considers an important problem of framing a response adaptive allocation design and analysing the resulting data when the responses are circular in nature. The proposed methodology is motivated and illustrated by a real-life example of cataract surgery. However, in real trials the responses are often delayed, covariates are presented,

or several treatments are used. Considering all these issues, relevant development is the concern for future development.

Acknowledgments

The authors are grateful to the editor, associate editor, and anonymous reviewers for their valuable suggestions, which helped to improve the quality of the article.

References

Atkinson, A. C., and A. Biswas. 2014. *Randomised response-adaptive designs in clinical trials*. Boca Raton, FL: CRC Press.

Biswas, A., and R. Bhattacharya. 2016. Response-adaptive designs for continuous treatment responses in phase III clinical trials: A review. *Statistical Methods in Medical Research* 25:81–100.

Bakshi, P. 2010. Evaluation of various surgical techniques in brunescent cataracts. Unpublished thesis, Disha Eye Hospital, West Bengal, India.

Bandyopadhyay, U., and R. Bhattacharya. 2016. An invariant allocation function for multi-treatment clinical trials. *Statistics and Its Interface* 9:1–10.

Bandyopadhyay, U., and A. Biswas. 2001. Adaptive designs for normal responses with prognostic factors. *Biometrika* 88:409–19.

Bartlett, R. H., D. W. Roloff, R. G. Cornell, A. F. Andrews, P. W. Dillon, and J. B. Zwischenberger 1985. Extracorporeal circulation in neonatal respiratory failure: A prospective randomized trial. *Pediatrics* 76:479–87.

Biswas, A. 2001. Adaptive designs for binary treatment responses in phase III clinical trials: Controversies and progress. *Statistical Methods in Medical Research* 10:353–64.

Biswas, A., and A. Dewanji. 2004. Inference for a RPW-type clinical trial with repeated monitoring for the treatment of rheumatoid arthritis. *Biometrical Journal* 46:769–79.

Biswas, A., S. Dutta, A. K. Laha, and P.K. Bakshi. 2015. Response-adaptive allocation for circular data. *Journal of Biopharmaceutical Statistics* 25:830–42.

Biswas, A., S. Dutta, A. K. Laha, and P. K. Bakshi. 2016. Comparison of treatments in a cataract surgery with circular response *Statistical Methods in Medical Research* 25:2238–2249. doi:10.1177/0962280213519717.

Hu, F., and L. X. Zhang. 2004. Asymptotic properties of doubly adaptive biased coin design for multi-treatment clinical trials. *Annals of Statistics* 32:268–301.

Jain, N. B., R. B. Wilcox III, J. N. Katz, and L. D. Higgins. 2013. Clinical examination of the rotator cuff. *PM & R* 5:45–56.

Jammalamadaka, S. R., and A. SenGupta. 2001. Topics in circular statistics. Singapore: World Scientific.

Mardia, K. V., and P. E. Jupp. 2000. Directional statistics. London, UK: John Wiley & Sons Ltd.

Rosenberger, W. F., and J. L. Lachin. 2016. Randomisation in clinical trials: Theory and practice, 2nd ed. New York, NY: Wiley.

Sverdlov, O. 2016. An overview of adaptive randomization designs in clinical trials. In *Modern adaptive randomized clinical trials: Statistical and practical aspects*, ed. O. Sverdlov, 3–44. Boca Raton, FL: CRC Press.

Tamura, R. N., D. E. Faries, J. S. Andersen, and J. H. Heiligenstein. 1994. A case study of an adaptive clinical trial in the treatment of out-patients with depressive disorder. *Journal of the American Statistical Association* 89:768–76.