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An invariant allocation function for multi-treatment clinical trials

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An allocation function, invariant under monotonic transformation, is proposed in the context of multi-arm clinical trials for a class of continuous response distributions. The aim is to skew the allocation towards the most promising treatment using the whole information about the response distributions. A response adaptive implementation based on the proposed allocation function is suggested and assessed through some useful performance measures.

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1. INTRODUCTION

Ethics is always an important concern in clinical trials involving human beings. Naturally, favouring the best treatment for the allocation of patients becomes necessary. But the age old practice of assigning an equal number of subjects to each treatment arm does not discriminate the effects of the superior and the inferior treatments and hence is not preferred from an ethical perspective. Response adaptive randomization is often recommended in this context for its ability to skew the allocation towards more promising treatments on the basis of repeated analysis of the allocation and response data available so far. A number of allocation designs utilizing the intermediate data to find the more promising treatment is available in the literature. For binary treatment outcome, the popular method is to use urns where the urn composition is continuously updated based on the available data with a view to favour the better performing treatment for further allocation. A thorough review exploring the usefulness of urns for sequential treatment allocation can be found in [1]. However, in continuous response trials, the idea of *treatment effect mapping* [2] is mostly adopted where the chance of allocation for an entering subject is determined by some function of the available measures of the treatment effects. Such a function is chosen for ensuring higher allocation to the more promising treatment.

However, the one way strategy to promote the better performing treatment should not be the only objective for a good clinical trial. A minimum requirement may be to detect a little departure in treatment effectiveness most of the times, which in statistical language amounts to ensuring a higher power for a relevant test of hypothesis. Jennison and Turnbull [3] provided a unified way to achieve different aims within the same framework through a constrained optimization problem. Their suggestion resulted in a flurry of research activities exploring different optimal response adaptive designs. The earliest attempt [4] derived an optimal proportion minimising the total expected failures for binary responses and implemented through a response adaptive procedure. Further examples of optimal target based designs for binary responses can be found in the works of [5, 6, 7], among others. As a variant to the above approach, optimum design theory is used in a recent work to develop optimal allocation design [8]. The approach of [3] is also useful for the subsequent development when the responses are continuous. Considering different optimality criterion (e.g. total expected responses and total number of responses exceeding a clinically relevant threshold) a number of optimal allocation designs are developed [9, 10, 11, 12, 13, 14].

However, most of the available optimal allocation designs are developed for two treatments and are not straightforward to extend for several treatments. The only problem seems to define an appropriate function ensuring a specified level of statistical precision. In a recent work [15], the problem is solved by considering the non-centrality parameter of a suitable test of homogeneity as the statistical precision specifying function. With some additional constraints, a multi-treatment analogue of the Neyman allocation of survey sampling is obtained. The same approach is followed [16, 17] to derive optimal allocation for exponential and binary responses, respectively. Optimum design theory based approach for the derivation of optimal target in a multi-treatment set up is also found in the context of continuous responses [18, 19]. An alternative approach consisting several constraints for the development of multi-treatment optimal target allocations can be found in more recent work [20]. Further applications of the above methodologies are also found in time-to-event trials. The main references include the works of [21], where total expected hazards is minimized for exponential and Weibull distributions under uniform censoring, and [22, 23], which provides an optimum design theory based approach for the development of optimal targets.

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However, most of the optimal allocations are developed solely on the basis of the summary measures (e.g. mean and variance) and ignore other information about the response distributions. But, if we look at the exploratory data analysis of [24], the possibility of a heavy tailed response distribution is observed and hence, the summary measure based procedure may be inappropriate. Another drawback of the summary measure based allocation function is that it has to be derived afresh depending on the response distribution. That is, the allocation function for a normal response trial is of no use in a trial with log-normal response. The current work is a heuristic attempt to develop an invariant allocation function incorporating the whole information about the class of continuous response variables. We start with the definitions of a *promising treatment* and a measure of *treatment effectiveness* under a multi-treatment set up and explore the properties in Section 2. A sequential estimation based response adaptive randomization together with the derivation of some related asymptotics is also provided in Section 2. Numerical study investigating the performance of the proposed procedure for normal, exponential and Cauchy responses is given in detail in Section 3. Redesigning real clinical trials adopting the proposed allocation procedure and the related assessment can be found in Section 4. Section 5 concludes with a discussion.

2. THE ALLOCATION

2.1 The general allocation function

Consider a clinical trial involving t treatments with X_k denoting the potential outcome for a subject assigned to treatment $k = 1, 2, .., t$. Instead of considering a specific distribution for X_k, we assume that X_k has an absolutely continuous distribution with distribution function F_k. In clinical trials, often a higher [25] or a lower [26] response indicates a favourable situation. However, for the purpose of development we assume that a higher response indicates a favourable situation. Then from an ethical point of view, the largest fraction of subjects would receive the most promising treatment, the next largest fraction would receive the next promising treatment and so on. Now treatment s can be regarded as the *most promising* if it is capable of producing larger responses more frequently than its competitors. In particular, if X_s is stochastically larger than any $X_k (k \neq s)$, treatment s will become the most promising one. However, defining treatment effectiveness in terms of summary measures (e.g. mean or median) for a general class of distributions does not always make sense as the information on the whole distribution is ignored. For the sake of illustration, we consider two treatments, say, treatments 1 and 2. Then the effect of treatment 1 relative to treatment 2 can be measured by $\pi_1 = P(X_1 > X_2)$. Naturally, treatment 1 is more effective than treatment 2 if $P(X_1 > X_2) > P(X_2 > X_1)$ or, equivalently $\pi_1 > \frac{1}{2}$, and the treatments are equally effective if $\pi_1 = \frac{1}{2}$. For example, if the response variable for the k th treatment is normal with mean μ_k and variance σ^2, the above expression reduces to the allocation given by [27] with the allocation function

$$\pi_1 = 1 - \pi_2 = \Phi\left(\frac{\mu_1 - \mu_2}{\sqrt{2}\sigma}\right)$$

having the tuning constant $\sqrt{2}\sigma$, where $\Phi(.)$ denotes the distribution function of a standard normal variable. Clearly, π_1 gives a *treatment effect mapping* where the treatment effect measure and the function of mapping are dictated by the distribution of responses itself. A simple analogy to the above suggests to use the quantity

$$\pi_s \quad = \quad P(X_s > X_k, k = 1, 2, .., t, k \neq s)$$

to measure the relative *effectiveness* of treatment s in a multi-treatment set up. Now π_s can be expressed as

$$\pi_s = \int \left\{ \prod_{k(\neq s)} F_k(x) \right\} dF_s(x),$$

which, through integration by parts, gives

$$\begin{aligned} \pi_s &= 1 - \sum_{r(\neq s)=1}^{t} \int \left\{ \prod_{k(\neq r)} F_k(x) dF_r(x) \right\} \\ &= 1 - \sum_{r(\neq s)=1}^{t} \pi_r \end{aligned}$$

so that $\sum_{k=1}^{t} \pi_k = 1$. Thus treatment s will be the *most effective* if $\pi_s > \pi_k$ for every $s(\neq k) = 1, 2, ..., t$, which simply implies that $\pi_s > \frac{1}{t}$. Again all the treatments will be *equally effective* if

$$\pi_1 = \pi_2 = ... = \pi_t = \frac{1}{t}.$$

In particular, when X_s is stochastically larger than $X_{s'}$, that is, treatment s is more promising than treatment s' then we have

$$\begin{aligned} \pi_s &= \int \left\{ \prod_{k(\neq s)} F_k(x) \right\} dF_s(x) \\ &= \int [1 - F_s(x)] d \left(\prod_{k(\neq s)} F_k(x) \right) \\ &\geq \int [1 - F_{s'}(x)] d \left(\prod_{k(\neq s)} F_k(x) \right) \\ &= \int \left(\prod_{k(\neq s)} F_k(x) \right) dF_{s'}(x) \\ &\geq \int \left(\prod_{k(\neq s')} F_k(x) \right) dF_{s'}(x) = \pi_{s'}. \end{aligned}$$

Moreover, when $F_1(x) = F_2(x) = ... = F_t(x)$ for all x, that is, if the treatments are equally promising then we get

$$\pi_s = \int [F_1(x)]^{t-1} dF_1(x) = \frac{1}{t}$$

for $s = 1, 2, .., t$. Therefore, if treatment s is the most promising then the proposed effectiveness measure is not only the highest but also higher than $\frac{1}{t}$, the effectiveness measure for equally effective treatments. It also follows that, if the treatments are ordered according to effectiveness, the corresponding measures of effectiveness also maintain the same ordering.

However, if a lower response indicates a favourable clinical situation, we need to assign the lowest(highest) fraction of subjects to the treatment having the highest(lowest) response, and hence we can fix up the allocation strategy by using the functions

$$(1) \qquad \pi_s^* = P\left(X_s < X_k, k = 1, 2, .., t, k \neq s\right).$$

$\pi_s^*, s = 1, 2, .., t$, as earlier, can be ordered according to treatment effectiveness. Another interesting feature of the relative effectiveness measure π_s(or π_s^*) is that it remains unchanged under a monotonic transformation of the response variables. The sensitivity of the defined measure in clinically relevant situations, therefore, suggests to use the collection $\{\pi_s($ or $\pi_s^*), s = 1, 2, .., t\}$ to fix up a multi-treatment ethical allocation strategy for a general system of continuous response distributions.

2.2 The allocation in practice

Although the allocation function has the capability of assigning subjects ethically without requiring the assumption of the existence of moments it can not be implemented in practice unless the response distributions are known to the experimenter. We assume that the response distributions are distinct and have a common support and specifically, the response to treatment k has the density $f_k(x, \boldsymbol{\theta}_k)$, for almost all x, $k = 1, 2, .., t$, where $\boldsymbol{\theta}_k$ is a $d(\geq 1)$ component vector of parameters with elements $\theta_{kj}, j = 1, 2, .., d$. We further assume that the densities are distinct with a common support. Then π_s can be looked upon as a function of the unknown parameters, say $\pi_s(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, ..., \boldsymbol{\theta}_t)$. Naturally, it would be reasonable to use sequentially updated estimates of the allocation function at every intermediate stage of the trial for the selection of a treatment to assign an entering subject. The trial starts with assigning an initial number n_0 of subjects to each treatment arm to start the response adaptive randomization from the $(tn_0 + 1)$ th entering subject. If $\delta_{k,i}$ is the allocation indicator of the i th entering subject (=1; if the subject is assigned to treatment k and =0; otherwise), X_{ki} denotes the potential response if the i th subject assigned to treatment k and $\mathcal{F}_j$ is the sigma algebra generated by $\{\delta_{k,i}, X_{ki}, k = 1, 2, .., t; 1 \leq i \leq j\}$ then a multi-treatment response adaptive allocation can be defined by the following allocation probabilities:

$$P(\delta_{k,i+1} = 1 \mid \mathcal{F}_i) = \pi_k(\widehat{\boldsymbol{\theta}}_{1i}, \widehat{\boldsymbol{\theta}}_{2i}, ..., \widehat{\boldsymbol{\theta}}_{ti}), i \geq tn_0,$$

where $\pi_k(\widehat{\boldsymbol{\theta}}_{1i}, \widehat{\boldsymbol{\theta}}_{2i}, ..., \widehat{\boldsymbol{\theta}}_{ti})$ is the maximum likelihood estimate of π_k based on the available response and allocation history prior to the entrance of the $(i + 1)$ th subject. In practice, $\widehat{\boldsymbol{\theta}}_{ki}$ with elements $\widehat{\theta}_{kji}, j = 1, 2, .., d$, is the solution of the equations $\frac{\partial \mathcal{L}_i}{\partial \boldsymbol{\theta}_k} = \mathbf{0}$, where $\mathcal{L}_i = \mathcal{L}_i(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, ..., \boldsymbol{\theta}_t) = \prod_{j=1}^{i} \prod_{k=1}^{t} \{f_k(X_{kj}, \boldsymbol{\theta}_k)\}^{\delta_{k,j}}$ denotes the likelihood of the data after i responses are observed.

However, it would be worthwhile to mention that response adaptive designs, in general, increase the variability of the allocation. But such variability has strong influence on statistical precision (e.g. power of a relevant test) and, in particular, the lower variability increases the power [5]. Therefore, we need to design the allocation to keep the variability at a lower level. A sensible suggestion, in this context, is to adopt a suitable doubly adaptive biased coin design [28] for reducing variability and achieve the desired target allocation proportion in the limit. However, in the current work, we continue the development with sequentially estimated response adaptive designs.

2.3 Limiting proportion of allocation

For an assessment of allocation procedure prior to implementation, we need to examine the procedure in the limit. For the derivation of the asymptotic properties, we impose the following regularity conditions on the response distribution for every $k = 1, 2, .., t$.

A1. There exists an open subset ω of the parameter space Θ containing the true parameter.

A2. For almost all x, $f_k(x, \boldsymbol{\theta}_k)$ admits all third order derivatives $\frac{\partial^3 f_k(x, \boldsymbol{\theta}_k)}{\partial \theta_{kl} \partial \theta_{kr} \partial \theta_{ks}}$ for all $\boldsymbol{\theta}_k \in \omega$. Moreover, the integral $\int f_k(x, \boldsymbol{\theta}_k) dx$ is twice differentiable with respect to each element of $\boldsymbol{\theta}_k$ under the integral sign and the first partials have finite moments of order $2 + \eta$ for some $\eta > 0$.

A3. There exists functions M_{klrs} such that for almost all x

$$\left| \frac{\partial^3 log f_k(x, \boldsymbol{\theta}_k)}{\partial \theta_{kl} \partial \theta_{kr} \theta_{ks}} \right| < M_{klrs}(x)$$

for all $\boldsymbol{\theta}_k \in \omega$, where

$$E_{\boldsymbol{\theta}_k} \{M_{klrs}(X_{k1})\} < \infty$$

for all l, r, s.

A4. $\pi_k(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, ..., \boldsymbol{\theta}_t)$ is a continuous function.

If $N_{kn} = \sum_{j=1}^{n} \delta_{k,j}$ denotes the observed number of allocations to treatment k out of n assignments following the proposed response adaptive methodology, then we have the following result.

Result 1: *As* $n \to \infty$,

$$N_{kn} \to \infty,$$

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

Proof: We start with the fact that $N_{kn} = \sum_{j=1}^{n} \delta_{k,j}$ is nondecreasing in n for each k, and hence converges almost surely to $\sup_n N_{kn}$, which is either finite or $+\infty$. But as $N_{1n} + N_{2n} + ... + N_{tn} = n$, N_{kn} can not be finite for all k and hence $N_{kn} \to \infty$ for some k. Let us define

$$G = \left\{ k : \sup_n N_{kn} = +\infty, k = 1, 2, .., t \right\},$$

which by construction is non empty.

Since for every $k \in G$, $N_{kn} \to \infty$ almost surely, we have, under A1–A3, as $n \to \infty$, $\widehat{\boldsymbol{\theta}}_{kn} \to \boldsymbol{\theta}_k$ almost surely [29] for each $k \in G$. But for every $k \notin G$, $\sup_n N_{kn} < \infty$ almost surely and hence $\widehat{\boldsymbol{\theta}}_{kn}, k \notin G$ becomes fixed almost surely after finite n. Therefore, for any $k \in \{1, 2, .., t\}$, $\widehat{\boldsymbol{\theta}}_{kn}$ converges almost surely to some finite quantity and hence, in view of condition A4, $\pi_k(\widehat{\boldsymbol{\theta}}_{1n}, .., \widehat{\boldsymbol{\theta}}_{tn})$ converges almost surely to a finite quantity $\pi_k^* \in (0, 1), k = 1, 2, .., t$. Finally the representation

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

together with the martingale convergence theorem [30], gives

$$\frac{N_{kn}}{n} \to \pi_k^*,$$

and hence, as $n \to \infty$, $N_{kn} \to \infty$ almost surely for each k. □

As a consequence of the above result and the fact that for each k, the allocation function $\pi_k(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, ..., \boldsymbol{\theta}_t)$ is continuous, we get the following result.

Result 2: *As* $n \to \infty$,

$$\frac{N_{kn}}{n} \to \pi_k(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, ..., \boldsymbol{\theta}_t)$$

almost surely, $k = 1, 2, .., t$.

Note: The above result ensures the assignment according to the degree of superiority of the treatments at least in the limit.

Result 3: *For any* $k = 1, 2, .., t$, *as* $n \to \infty$,

$$\sqrt{n}(\widehat{\boldsymbol{\theta}}_{kn} - \boldsymbol{\theta}_k) \to N_d(\mathbf{0}, [\pi_k I_k(\boldsymbol{\theta}_k)]^{-1}),$$

in distribution, where $N_d(\boldsymbol{\mu}, \Sigma)$ *represents d-variate normal distribution with mean vector* $\boldsymbol{\mu}$ *and dispersion matrix* Σ, $\pi_k = \pi_k(\boldsymbol{\theta}_1, \boldsymbol{\theta}_2, ..., \boldsymbol{\theta}_t)$ *and*

$$I_k(\boldsymbol{\theta}_k) = E_{\boldsymbol{\theta}_k} \left\{ \frac{\partial \ln f_k(X_{k1}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k} \frac{\partial \ln f_k(X_{k1}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k^T} \right\}$$

is the $d \times d$ *positive definite Fisher information matrix associated with the distribution of* X_{k1}.

Proof: Writing $L_n(\boldsymbol{\theta}_k) = \prod_{j=1}^{n} \{f_k(X_{kj}, \boldsymbol{\theta}_k)\}^{\delta_{k,j}}$, we observe that

$$\frac{\partial log L_n(\boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k} = \sum_{j=1}^{n} \delta_{k,j} \frac{\partial log f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k} \tag{2}$$

and

$$\frac{\partial^2 log L_n(\boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k \partial \boldsymbol{\theta}_k^T} = \sum_{j=1}^{n} \delta_{k,j} \frac{\partial^2 log f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k \partial \boldsymbol{\theta}_k^T}.$$

Since

$$\sum_{j=1}^{n} \left\{ \delta_{k,j} \frac{\partial^2 log f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k \partial \boldsymbol{\theta}_k^T} - E\left(\delta_{k,j} \frac{\partial^2 log f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k \partial \boldsymbol{\theta}_k^T} | \mathcal{F}_{j-1} \right) \right\}$$

is a martingale, it follows from martingale convergence theorem [30] together with Result 2, that as $n \to \infty$,

$$B_n = \frac{1}{n} \frac{\partial^2 log L_n(\boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k \partial \boldsymbol{\theta}_k^T} \to -\pi_k I_k(\boldsymbol{\theta}_k) \tag{3}$$

almost surely. Now, using the fact that $\frac{\partial log \mathcal{L}_n(\boldsymbol{\theta}_k)}{\partial \widehat{\boldsymbol{\theta}}_k}$ vanishes at $\boldsymbol{\theta}_k = \widehat{\boldsymbol{\theta}}_{kn}$, Taylor expansion at the true value of $\boldsymbol{\theta}_k$ yields

$$\frac{1}{\sqrt{n}} \frac{\partial log \mathcal{L}_n(\boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k} + (B_n + C_n)\sqrt{n}(\widehat{\boldsymbol{\theta}}_{kn} - \boldsymbol{\theta}_k) = \mathbf{0}, \tag{4}$$

where B_n is given by (3), and C_n is the matrix of elements

$$c_{lrn} = \frac{1}{2} \sum_{s=1}^{d} (\widehat{\theta}_{ksn} - \theta_{ks}) \left\{ \frac{1}{n} \sum_{j=1}^{n} \delta_{k,j} \frac{\partial^3 f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \theta_{kl}^* \partial \theta_{kr}^* \partial \theta_{ks}^*} \right\},$$
$$l, r = 1, 2, .., d$$

with $\{\theta_{kl}^*, \theta_{kr}^*, \theta_{ks}^*\}$ as the elements of $\boldsymbol{\theta}_k^*$, a point on the line segment joining $\boldsymbol{\theta}_k$ and $\widehat{\boldsymbol{\theta}}_{kn}$.

By A3, together with martingale convergence theorem [30] and Result 2, we get

$$\left| \frac{1}{n} \sum_{j=1}^{n} \delta_{k,j} \frac{\partial^3 f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \theta_{kl}^* \partial \theta_{kr}^* \partial \theta_{ks}^*} \right| \leq \frac{1}{n} \sum_{j=1}^{n} \delta_{k,j} M_{klrs}(X_{kj}),$$

which, as $n \to \infty$, converges almost surely to $\pi_k E\{M_{klrs}(X_{k1})\} (< \infty)$. Hence, as $\widehat{\boldsymbol{\theta}}_{kn} \to \boldsymbol{\theta}_k$ almost surely, we have

$$C_n \to O^{d \times d} \tag{5}$$

in probability. Now by virtue of A2, A3 and the multivariate martingale Central limit Theorem (see, for example, Appendix A of [31]), we have as $n \to \infty$,

$$\frac{1}{\sqrt{n}} \sum_{j=1}^{n} \delta_{k,j} \frac{\partial log f_k(X_{kj}, \boldsymbol{\theta}_k)}{\partial \boldsymbol{\theta}_k} \to N_d(\mathbf{0}, \pi_k I_k(\boldsymbol{\theta}_k)), \tag{6}$$

in distribution. Finally the required result follows from (4), using (3), (5) and (6). □

3. ASSESSING THE PERFORMANCE

In the context of clinical trials, normal, exponential and Cauchy responses are popularly used to model the responses and hence we assume these response models to examine the performance of the proposed allocation procedure. Specifically, we assume that the response distribution corresponding to the k th treatment can be expressed as $F(\sigma_k^{-1}(x-\mu_k))$, where F is either normal or exponential or Cauchy. Then π_k is nothing but a function of the unknown parameter vectors $\boldsymbol{\theta}_k = (\mu_k, \sigma_k)^T, k = 1, 2, .., t$. As earlier, we use sequentially updated maximum likelihood estimates of the allocation probabilities for the allocation of incoming subjects.

Although the results of the previous section ensured desirable behaviour in the limit, the performance in small samples is yet to be assessed. For the assessment in small samples, we consider three treatments and calculate the following measures:

- The distribution of allocation to different treatments.
- The power of a relevant test of equality of treatment effects.

We simulate the expected values of $\frac{N_{sn}}{n}$, denoted by $EAP_s, s = 1, 2, 3$ together with the standard errors for different responses considering more general situations. In addition, we carry out the likelihood ratio test to calculate the power under specific alternatives.

3.1 Normal responses

Suppose the response on treatment k has a normal distribution with mean μ_k and variance $\sigma_k^2, k = 1, 2, 3$. In such case, writing $\rho_s = \frac{\sigma_s^2}{\sqrt{(\sigma_s^2+\sigma_k^2)(\sigma_s^2+\sigma_{k'}^2)}}$, $\pi_s(s \neq k, k^{'} = 1, 2, 3)$ can be simplified to

$$\pi_s = \Phi_2\left(\frac{\mu_s - \mu_k}{\sqrt{\sigma_s^2+\sigma_k^2}}, \frac{\mu_s - \mu_{k'}}{\sqrt{\sigma_s^2+\sigma_{k'}^2}}, \rho_s\right), s = 1, 2, 3,$$

where $\Phi_2(.,.,\rho)$ is the distribution function of a bivariate normal variable with means zero, variances unity and correlation coefficient ρ. For the allocation of the current subject, we use the maximum likelihood estimates based on the available data in the above expression to determine the corresponding allocation probability. Evaluation of any response adaptive allocation has two aspects, namely, ethical and inferential. We consider a multi-treatment generalisation [32] of the allocation design by [27] as a relevant competitor in terms of ethics. The corresponding allocation function is

$$\pi_s^{BC} = \frac{1}{3}\Phi\left(\frac{\mu_s - \mu_k}{\sqrt{\sigma_s^2+\sigma_k^2}}\right) + \frac{1}{3}\Phi\left(\frac{\mu_s - \mu_{k'}}{\sqrt{\sigma_s^2+\sigma_{k'}^2}}\right),$$

$s(\neq k, k') = 1, 2, 3$, where $\Phi(.)$ is the distribution function of a standard normal variable and BC is formed by the acronym of the authors. Now, if we assume that the responses from different treatments are equally variable, equal allocation gives the highest power for the likelihood test procedure.

Naturally, equal allocation must be included in the list of competitors when the intention is also to assess the possible inferential gain of the proposed allocation. In particular, we have determined the sample size required under equal allocation to reach 80% power using the likelihood ratio test for a specified shift from the null value with a common scale value $\sigma = 1$ and evaluate the performance at this sample size. Sample sizes for specified departure from the equivalence and the relevant performance measures, both exact and asymptotic, are reported in Table 1.

Remarks: The numerical figures of Table 1 are obtained by a simulation study with 10,000 iterations. The relevant figures depict that the proposed allocation assigns subjects according to the order of treatment effectiveness. That is, the highest allocation to the most promising treatment (i.e. the treatment with the highest mean response in this case), and the lowest allocation to the least promising treatment (i.e. the treatment with the lowest mean response in this case). We also find that the allocation proportion for the proposed allocation is always higher than the competitor and these values are close to the corresponding limiting values.The proposed allocation is an improvement over the equal allocation and the competitor in terms of allocation proportion, but a loss in power is observed in general. Actually, skewing the allocation towards the most promising treatment for further allocation causes, in general, a loss in power. For the proposed allocation, higher(lower) fraction of subjects is assigned to the most(least) promising treatment and consequently a loss in power is observed. However, such an inferential loss (i.e. loss in power) can be compromised if we look at the significant gain in ethical norms (i.e. higher observed allocation proportions). Thus, apart from assigning a larger fraction of subjects to the promising treatments, the proposed allocation also detects a departure from the equivalence with high probability even under more general situations.

3.2 Exponential responses and censoring

Exponential distribution plays an important role in modelling the survival related outcomes. In the current context, if the response to treatment k has an exponential distribution with mean $\sigma_k, k = 1, 2, 3$ then a routine algebra expresses π_s as

$$\pi_s = \frac{\sigma_s^2(2\sigma_k\sigma_{k'} + \sigma_s\sigma_k + \sigma_s\sigma_{k'})}{(\sigma_s+\sigma_k)(\sigma_s+\sigma_{k'})(\sigma_k\sigma_{k'} + \sigma_s\sigma_k + \sigma_s\sigma_k)}, s \neq (k, k').$$

The performance investigation of the resulting allocation design is a routine follow up and hence we skip the details.

Table 1. Performance at 80% power with $\sigma = 1$ and $H_0 : \mu_1 = \mu_2 = \mu_3 = 1.0$

Alternative (μ_1, μ_2, μ_3)	n	**Allocation Design**	**Expected Allocation Proportion** $EAP_1(SD)$	$EAP_2(SD)$	$EAP_3(SD)$	**Power**
(1.5,1.0,1.0)	179	**Proposed**	.488(.08) **.482**	.256(.07) **.259**	.256(.07) **.259**	.821
		Biswas & Coad	.426(.06) **.426**	.287(.06) **.287**	.287(.06) **.287**	.824
(1.5,1.5,1.0)	176	**Proposed**	.399(.09) **.397**	.396(.08) **.397**	.204(.11) **.206**	.659
		Biswas & Coad	.379(.09) **.379**	.377(.06) **.379**	.243(.09) **.242**	.665
(1.7,1.0,1.0)	95	**Proposed**	.550(.09) **.544**	.225(.09) **.228**	.225(.09) **.228**	.807
		Biswas & Coad	.460(.08) **.460**	.270(.08) **.270**	.270(.08) **.270**	.819
(1.7,1.7,1.0)	94	**Proposed**	.416(.09) **.417**	.418(.09) **.417**	.166(.09) **.166**	.587
		Biswas & Coad	.396(.07) **.396**	.396(.07) **.396**	.208(.07) **.208**	.642
(1.7,1.5,1.0)	117	**Proposed**	.460(.10) **.457**	.357(.10) **.359**	.183(.07) **.184**	.667
		Biswas & Coad	.416(.07) **.415**	.360(.07) **.360**	.222(.07) **.225**	.711
(2.0,1.5,1.0)	63	**Proposed**	.543(.11) **.548**	.298(.09) **.300**	.159(.10) **.152**	.667
		Biswas & Coad	.460(.09) **.466**	.334(.09) **.330**	.206(.08) **.204**	.713
(2.0,1.5,1.5)	179	**Proposed**	.488(.09) **.482**	.256(.08) **.259**	.256(.08) **.259**	.829
		Biswas & Coad	.426(.07) **.425**	.287(.06) **.287**	.287(.06) **.288**	.831

Boldface values indicate the corresponding limiting values.
EAP values for the equal allocation are always 0.333 with SD around .05.

However, we investigate the performance in a more general situation when few of the responses are censored. To be specific, let T_k and C_k be, respectively, the survival time and the censoring time corresponding to subjects assigned to treatment k. Then for every such subject, we only observe (X_k, I_k), where $X_k = \min(T_k, C_k)$ and $I_k = 1$ or 0 according as $T_k < C_k$ or $T_k \geq C_k$. If a higher response is favourable then an analogue to π_s under the presence of censoring can be defined as

$$\pi_s^c = \quad P(X_s > X_k, k = 1, 2, .., t, k \neq s)$$

where c indicates the presence of censoring. Although a number of censoring schemes are available in the literature, we continue with a particular type of random censoring, namely, the Koziol-Green model of random censorship [33]. If F_k and G_k denote respectively the distribution functions of the lifetime and censoring variables corresponding to treatment k, then under the assumption of Koziol-Green model

(a) T_k and C_k are independent.

(b) $1 - G_k(t) = \{1 - F_k(t)\}^{\gamma_k}, \quad k = 1, 2, .., t, \quad \gamma_k > 0.$

Under the above assumptions, the censoring indicator I_k does not contain Fisher information about the parameters of the lifetime distribution and moreover, permits convenient inferential operations. However, we continue with the earlier assumption of exponential response together with the assumption that $\gamma_k = \gamma$ for every k. Then it is interesting to observe that the expression of π_s^c is identical with π_s, just mentioned above. For the evaluation of the performance, we start with the calculation of sample size required for equal allocation to reach 90% power using the likelihood ratio test for a specified shift from the null value with a fixed $\gamma = 1$ and explore the performance at this sample size. Sample sizes for specified departure from the equivalence and the relevant performance measures are reported in Table 2.

Remarks: The performance measures of Table 2 are obtained from a simulation study with 10,000 replications. As expected, the observed fraction of subjects assigned to each treatment are in accordance with the effectiveness of treatments. That is, the highest observed fraction to the most promising treatment (i.e. the treatment with the highest

Table 2. Performance at 90% power under censoring with $\gamma = 1$ and $H_0 : \sigma_1 = \sigma_2 = \sigma_3$

Alternative		**Expected Allocation Proportion**			**Power**
$(\sigma_1, \sigma_2, \sigma_3)$	n	$EAP_1(SD)$	$EAP_2(SD)$	$EAP_3(SD)$	
(2,1,1)^a	120	0.531 (0.1)	0.233 (0.09)	0.236 (0.09)	0.852
(2,2,1)^a	127	0.415 (0.11)	0.414 (0.1)	0.171 (0.08)	0.573
(2.5,1,1)^a	73	0.576 (0.12)	0.214 (0.1)	0.211 (0.1)	0.853
(4,2,2)^b	123	0.534 (0.11)	0.233 (0.09)	0.233 (0.09)	0.864
(4,3,2)^b	160	0.472 (0.09)	0.335 (0.09)	0.193 (0.08)	0.751
(4,4,2)^b	125	0.413 (0.10)	0.415 (0.1)	0.171 (0.08)	0.584
(5,4,2)^b	72	0.58 (0.11)	0.211 (0.10)	0.209 (0.10)	0.866
(5,3,2)^b	95	0.527 (0.11)	0.296 (0.11)	0.177 (0.09)	0.776
(5,3,3)^b	225	0.484 (0.08)	0.258 (0.08)	0.257 (0.08)	0.884

For $a(b)$ the common value under the null hypothesis is 1(2).
EAP values for the equal allocation are always 0.333 with SD around .05.

mean response in this case) and the lowest fraction to the least promising treatment (i.e. the treatment with the lowest mean response in this case). But such unbalanced allocation resulted in a loss of power as compared to that of equal allocation. However, such a loss can be compensated at the cost of ability of assigning a higher fraction of subjects to the effective treatments. The conclusion remains valid even if we vary the configuration under the null hypothesis. Now it is interesting to note that neither the allocation probability for any incoming subject nor the likelihood ratio test statistic depends on the estimated γ. Therefore, without any loss of generality, γ can be chosen as unity. However, inclusion of γ keeps the essence of censoring.

3.3 Cauchy responses

As indicated earlier, Cauchy response is relevant in the context of clinical trials though it is of limited use. However, the proposed allocation can also be adopted even for Cauchy responses. Therefore, in addition, we provide the performance measures when the response to treatment k has a Cauchy distribution with median response μ_k and scale parameter σ. It can be observed that

$$\begin{aligned}\pi_1 &= \int_{-\infty}^{\infty} P(X_2 < x, X_3 < x) f_1(x, \mu_1, \sigma_1) dx \\ &= \frac{\sigma}{\pi} \int_{-\infty}^{\infty} \prod_{k=2,3} \left\{ \frac{1}{2} + \frac{1}{\pi} \arctan\left(\frac{x - \mu_k}{\sigma}\right) \right\} \frac{dx}{\sigma^2 + (x - \mu_1)^2}.\end{aligned}$$

But further simplification was not possible and hence we relied on numerical methods to calculate the allocation probabilities $\pi_s, s = 1, 2, 3$ for specific parameter values. As before, we sequentially update the maximum likelihood estimates to determine the allocation probability for the next entering subject. But no closed form solution is obtainable from the likelihood equations and hence requires iterative procedures to obtain the estimates. Since we did not find any existing multi-treatment allocation design with Cauchy responses, the traditional equal allocation is considered as a reasonable competitor to determine the degree to which the proposed allocation is an improvement. We, therefore, provide the EAP values, corresponding limiting proportions and statistical power in Table 3 for specific choices of the parameters.

Remarks: A simulation study with 10,000 iterations generated the numerical figures of Table 3. As expected, the proposed allocation randomizes the highest fraction of subjects to the most promising treatment (i.e. the treatment with the highest median in this case), and the lowest fraction to the least promising treatment (i.e. the treatment with the lowest median in this case). Although, skewed allocation causes, in general, a loss in power, but such a loss is not uniform and some exceptions are also possible. For example, a close examination of the figures of Table 3 reveals few instances, in which equal allocation is underpowered than the response adaptive design. Such a behaviour is also noted in the context of a nonparametric response adaptive allocation design [10]. But heavy tails of the Cauchy responses made the convergence of the simulated allocation proportions to the limiting values slower, and hence higher allocation proportion is expected in large clinical trials. Such an encouraging performance of the proposed procedure is always desired from a practitioner's point of view.

3.4 Other responses

The purpose of the proposed allocation function is twofold, namely, to provide an ethical allocation when the moments of the response distribution is not finite and to keep the allocation function unchanged even when monotonic transformations of the original response variables are used to model the response. In real clinical trials, we often come across such a situation. For example, in clinical trials on "hypertension", the response variable is the blood pressure of the entering individual, and the response distribution is assumed log normal [34], in general. Then it is interesting to note that if we have the expression of π_s for normal treatment responses, the same π_s will serve as the allocation

Table 3. Performance evaluation for $n = 120$ with $H_0 : \mu_1 = \mu_2 = \mu_3$

Alternative	**Expected Allocation Proportion**			**Power**
$(\mu_1, \mu_2, \mu_3, \sigma)$	$EAP_1(SD)$	$EAP_2(SD)$	$EAP_3(SD)$	
(1.8,1,1,1.0)	0.4 (0.06)	0.298 (0.052)	0.302 (0.052)	0.185
	0.465	**0.267**	**0.267**	.158
(2.2,1,1,1.0)	0.449 (0.055)	0.276 (0.048)	0.275 (0.047)	0.648
	0.527	**0.236**	**0.236**	.536
(2.6,1,1,1.0)	0.498 (0.057)	0.249 (0.046)	0.252 (0.046)	0.969
	0.582	**0.209**	**0.209**	.898
(1.4,1,1,0.5)	0.398 (0.057)	0.301 (0.052)	0.301 (0.052)	0.193
	0.465	**0.267**	**0.267**	.159
(1.6,1,1,0.5)	0.448 (0.058)	0.275 (0.049)	0.277 (0.049)	0.662
	0.527	**0.236**	**0.236**	.538
(2.2,1,.7,0.5)	0.475 (0.078)	0.274 (0.061)	0.241 (0.054)	0.939
	0.692	**0.178**	**0.130**	.953
(2.8,2,2,1.0)	0.414 (0.055)	0.293 (0.047)	0.293 (0.05)	0.225
	0.465	**0.267**	**0.267**	.142
(3.0,2,2,1.0)	0.442 (0.055)	0.278 (0.047)	0.28 (0.048)	0.541
	0.497	**0.251**	**0.251**	.357
(2.6,2,2,0.5)	0.447 (0.057)	0.275 (0.048)	0.278 (0.049)	0.674
	0.527	**0.236**	**0.236**	.569
(2.2,1.2,.8,0.5)	0.483 (0.077)	0.269 (0.059)	0.248 (0.054)	0.951
	0.663	**0.204**	**0.133**	.967

The minimum value of (μ_1, μ_2, μ_3) in the first column gives the common value under the null hypothesis.
Boldface figures indicate the corresponding limiting values.
EAP values for the equal allocation are always 0.333 with SD around .04.
Second figures in each cell in the power column give those for equal allocation.

function when the response is log-normal. This is because, normal and log normal variates are related by a monotonic transformation. In survival related trials, exponential, extreme value and Weibull are the most commonly used distributions for response variable. It is well known that a Weibull variate can be obtained through a power transformation of an exponential variate and the logarithm of a Weibull variate has an extreme value distribution. Therefore, if π_s is available for exponentially distributed responses, it will continue to act as the allocation function for equishaped Weibull or extreme value responses due to the invariance of the allocation function under monotonic transformation. The same conclusion remains valid even under the Koziol-Green model of censoring.

4. REDESIGNING A REAL CLINICAL TRIAL: CONVERGENCE INSUFFICIENCY TRIAL

It was a randomized, multi-center clinical trial [35] involving $n = 40$ adults with symptomatic *convergence insufficiency* (CI). The patients were randomly assigned to receive either of the three treatments, namely, *office-based vision therapy/orthoptics* (**Treatment 1**), *office-based placebo vision therapy/orthoptics* (**Treatment 2**), or *home-based pencil pushups* (**Treatment 3**). To measure the symptoms and changes in symptoms, the score on the CI Symptom Survey-V15 was used as the primary outcome measure. A treatment is considered beneficial if it causes a significant reduction of the CI Symptom Score. Although patients in all three treatment arms demonstrated improvement in symptoms but only the patients receiving Treatment 1 show statistically and clinically significant changes. After 12 weeks of treatment, the means and standard deviations (within braces) of the CI Symptom Survey-V15 scores were calculated and reported as 20.7(10.2) for Treatment 1, 25.2(10.3) for Treatment 2 and 26.5(7.3) for Treatment 3. Treating these as the true values, we redesign the trial using the proposed allocation procedure assuming normality of responses. Since a lower response is favourable, we use equation (1) and perform 10,000 iterations of the allocation procedure with $n = 40$ patients. We assume that the responses are readily available and update the allocation probabilities after each response is observed. On an average, the simulation results in the assignment of 21, 11 and 8 subjects, respectively, to **Treatment 1**, **Treatment 2** and **Treatment 3** as compared to the actual allocation numbers 12, 13 and 15. That is, on an average, almost 50% of the patients would receive the best treatment if the proposed allocation had been used. Although the redesigning results in encouraging performance, it can not be generalized as the trial is a smaller one recruiting only 40 patients and the outcomes are not immediate. However, in case some of the responses are delayed, we can still apply the proposed allocation without affecting the asymptotic properties if we randomize an incoming subject based on the data, available so far.

5. CONCLUDING REMARKS

The effectiveness of the proposed allocation, in preserving both the statistical and ethical norms for a broad class of continuous responses, is investigated in the present work. However, at this point, it is interesting to note that skewed allocation, in general, faces a loss in power and maintaining the specified power level requires a larger number of accruals. But at the same time it reduces the risk of using a potentially harmful treatment. For the proposed allocation the loss in power is not significant in most of the cases but results in higher number of allocations to the promising treatments. Thus, looking at the gain in ethical benefits, one can recommend the proposed allocation in real situations. Though we have used the parametric set up for practical implementation, it would not be a difficult task to execute the allocation process by estimating the allocation functions using nonparametric methods. In particular, use of U statistics to estimate the allocation probability under a homoscedastic situation is always an appropriate alternative. However, the participants in a real clinical trial are often heterogeneous according to few covariates and the corresponding development of a sensible allocation function is a scope for future study.

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