Brazilian Journal of Probability and Statistics
2020, Vol. 34, No. 2, 291–303
https://doi.org/10.1214/18-BJPS427
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Adaptive two-treatment three-period crossover design for normal responses

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Abstract. In adaptive crossover design, our goal is to allocate more patients to a promising treatment sequence. The present work contains a very simple three period crossover design for two competing treatments where the allocation in period 3 is done on the basis of the data obtained from the first two periods. Assuming normality of response variables we use a reliability functional for the choice between two treatments. We calculate the allocation proportions and their standard errors corresponding to the possible treatment combinations. We also derive some asymptotic results and provide solutions on related inferential problems. Moreover, the proposed procedure is compared with a possible competitor. Finally, we use a data set to illustrate the applicability of the proposed design.

1 Introduction

Crossover trials assign two or more treatments sequentially to the same subject with two or more groups of subjects receiving different treatment sequences. The most commonly used crossover design with two treatments, say A and B, is the AB/BA design where some of the experimental units under trial receive treatment A in period 1 and another treatment B in period 2, whereas the others have B and then A. The pros and cons of AB/BA design are discussed in Senn (1994) and Jones and Kenward (2015). In absence of baseline measurements, AB/BA design suffers from several drawbacks. For example, (i) tests for carryover effect have low power since they are based on between-subject variation and (ii) the carryover effect, the treatment-by-period interaction effect and the sequence difference are all completely aliased with one another. To overcome these issues, several authors suggest higher order crossover designs with two treatments. See, for example, Patterson and Lucas (1959), Balaam (1968), Ebbutt (1984), Fleiss (1986) and Kabaila and Vicendese (2012). The advantages of using a higher order design are for its ability to obtain within subject estimators of the carryover effect or the treatment-by-period interaction effect and in some designs these estimators are not aliased with each other. Another point in favor of higher order design is that it is not necessary to assume that the subject effects are random variables in order to test for a difference between the carryover effects.

In usual crossover designs, as discussed earlier, the number of experimental units allotted to different treatment sequences are fixed in advance. But in clinical trials it would be ethical to allocate larger number of patients to the better treatment sequence. Some works in this direction are due to Kushner (2003), Liang and Carriere (2009), Bandyopadhyay, Biswas and Mukherjee (2009, 2012), Bandyopadhyay and Mukherjee (2015) and Liang et al. (2014). In the present work, we consider a two treatment three period design with four treatment sequences: ABA, ABB, BAA, BAB. This design was earlier considered by Ebbutt (1984) and

Key words and phrases. Adaptive crossover design, Balaam's design, carryover effect, ethical allocation, skewed allocation.

Received July 2016; accepted December 2018.

it was compared with an existing two treatment three period design allowing two sequences ABB and BAA as proposed by Patterson and Lucas (1959). But our design, unlike the equal allocation design by Ebbutt, use the information of the first two periods for allocation of a patient in period 3, and hence it ultimately results unequal allocations to the possible treatment sequences. Our three-period model of this present paper is an extension of the adaptive crossover design for normal responses of Bandyopadhyay and Mukherjee (2015) which is based on a two-period design.

We plan to organize the paper in the following way. In Section 2, we provide some probability measures for normal response variables and observe the nature of such functionals in the context of ethical design. We then propose an adaptive allocation rule on the basis of these functionals and give some related asymptotic results. In Section 3, we carry out a test for treatment effects. Section 4 demonstrates various numerical computations to compare the performance of the proposed design with that of its comparable competitor. The application of the proposed design is illustrated through a data study in Section 5. The paper ends with a discussion in Section 6.

2 Proposed adaptive crossover design and related asymptotic results

2.1 Preliminaries

Let A and B be two competing treatments in clinical trial. Suppose there is a fixed horizon of n patients for trial and the patients come to the clinic sequentially. The trial size n is determined from the cost to conduct the trial. Here, as in a standard two treatment two period crossover design, each entering patient is allotted to treatment sequence AB or BA for the first two periods. In period 3, each entering patient is randomized between A and B, and thus a patient under this trial receives one of the following treatment sequences: ABA, ABB, BAA, BAB. The potential outcome from each patient under such trial can then be represented by a three-component vector $\mathbf{X} = \{X_{k_1}, X_{k_1k_2}, X_{k_1k_2k_3}\}, k_1 \neq k_2, k_1, k_2, k_3 = A, B$. Note that the first component of this vector is the response to treatment A or B in period 1, the second component is that in period 2 corresponding to treatment B (followed by A) or to A (followed by B) and similarly for the third component. The present work is based on the following assumptions on the response variables:

(I) Moment assumptions:

M1. $E(X_{k_1}) = \mu_{k_1}, E(X_{k_1k_2}) = \mu_{k_2} + \phi_{k_1}, E(X_{k_1k_2k_3}) = \mu_{k_3} + \phi_{k_2}, k_1 \neq k_2, k_1, k_2, k_3 = A, B$. The parameters μ_A and μ_B represent, respectively, the effects of treatments A and B while the parameters ϕ_A and ϕ_B are for the carryover effects of treatments A and B. Here, we use between subject evaluation in which the analysis remains unaffected by the presence of possible period effects. As a result, we need not require to incorporate the period effect in the moment assumption.

M2. The response from each subject have constant variance (σ^2) and the pairs of responses from the same subject have constant covariances ($\rho\sigma^2$). Moreover, the responses from different subjects are independent.

(II) Distribution assumptions:

D1. X_{k_1} has normal distribution with mean μ_{k_1} and variance $\sigma^2, k_1 = A, B$.

D2. Given X_{k_1}, the random variable $X_{k_1k_2}$ has normal distribution with conditional mean $\mu_{k_2} + \phi_{k_1} + \rho(X_{k_1} - \mu_{k_1})$ and variance $\sigma^2(1-\rho^2), \rho^2 < \frac{1}{2}, k_1, k_2 = A, B, k_1 \neq k_2$.

D3. Given $\{X_{k_1}, X_{k_1k_2}\}$, the random variable $X_{k_1k_2k_3}$ has normal distribution with conditional mean $\mu_{k_3} + \phi_{k_2} + \frac{\rho}{1+\rho}(X_{k_1} - \mu_{k_1}) + \frac{\rho}{1+\rho}(X_{k_1k_2} - \mu_{k_2} - \phi_{k_1})$ and variance $\sigma^2(1-2\rho^2), k_1, k_2, k_3 = A, B; k_1 \neq k_2$.

In fact, combining all assumptions mentioned above, it can be seen that the random vector $(X_{k_1}, X_{k_1k_2}, X_{k_1k_2k_3})$ follows a trivariate normal distribution with mean vector $(\mu_{k_1}, \mu_{k_2} + \phi_{k_1}, \mu_{k_3} + \phi_{k_2})$ and dispersion matrix $\sigma^2 R$ where $R = ((1-\rho)I_3 + \rho\mathbf{1}\mathbf{1}')$ with I_3 as the identity matrix of order 3 and $\mathbf{1}$ as the vector with all the elements unity.

2.2 Reliability functional

In the third period, patients are allocated to the treatments A or B by using a reliability functional. Earlier, Bandyopadhyay and Mukherjee (2015) have used some reliability functionals in a two-treatment two-period crossover trial with four possible treatment combinations AA, AB, BA and BB. In our present study, we use the following reliability functional

$$\pi = P[X_A + X_{BA} > X_B + X_{AB}],$$

in which larger response indicates the promising treatment. By our assumptions, $X_A + X_{BA} - X_B - X_{AB}$ is normally distributed random variable with mean $2(\mu_A - \mu_B) + (\phi_B - \phi_A)$ and variance $4\sigma^2(1-\rho^2)$. Hence, we can write the above functional as

$$\pi = \Phi\left(\frac{(\mu_A - \mu_B) + \frac{1}{2}(\phi_B - \phi_A)}{\sqrt{\sigma^2(1-\rho)}}\right).$$

The motivation behind the choice of the above reliability functional is the fact that in simple two treatment two period crossover design with treatment sequences AB and BA, if treatment A is said to be better than treatment B, the occurrences of total response of a patient receiving treatment A is stochastically larger than that under treatment B. In terms of the notations introduced in the present paper the superiority of treatment A over treatment B can be expressed by the inequality $2(\mu_A - \mu_B) + (\phi_B - \phi_A) > 0$ which in turn implies that $\pi > \frac{1}{2}$. So the allocation design based on the reliability functional π is ethical in the sense that, when A is better than B, there is a fair chance (more than 50%) for a patient to receive A. Under equivalence of two treatments $\pi = \frac{1}{2}$, so π-based design is also balanced in that situation.

2.3 Proposed design

In practice π is unknown. So for implementing the allocation procedure, we need to estimate π from the available data. In the proposed design, we estimate π on the basis of data obtained in the first two periods. For this, corresponding to the ith entering patient under the trial, we define the pair of indicator variables $\{\delta(A, B, i), \delta(B, A, i)\}$ where $\delta(A, B, i) = 1 - \delta(B, A, i) = 1$ or 0 as the ith patient receives treatment sequence AB or BA. Using these assignment indicator variables, the response variables Z_i and U_i can be represented by

$$Z_i = \delta(A, B, i)X_{Ai} + \delta(B, A, i)X_{Bi}$$

and

$$U_i = \delta(A, B, i)X_{ABi} + \delta(B, A, i)X_{BAi},$$

where $\{X_{Ai}, X_{Bi}\}$ and $\{X_{ABi}, X_{BAi}\}$ are, respectively, the potential outcome vectors for the ith patient corresponding to $\{A, B\}$ in period 1 and $\{B, A\}$ in period 2. Now, to implement the allocation procedure, the entering patients in period 1 are randomized equally between the treatments A and B. The patients, who receive treatment $A(B)$ in period 1, are treated by treatment $B(A)$ in period 2. We estimate the components of parameter vector $\boldsymbol{\theta} = (\mu_A, \mu_B, \phi_A, \phi_B, \sigma^2, \rho)$ on the basis of the data $(\delta(A, B, i), Z_i, U_i)$, $i = 1, \ldots, n$. In the present work, we adopt the maximum likelihood (ML) method for estimating the unknown parameters. If $f_{k_1,k_2}(z, u)$ denotes the density of a bivariate normal distribution with

means μ_{k_1} and $\mu_{k_2} + \phi_{k_1}$, common variance σ^2 and the common correlation coefficient ρ, $k_1 \neq k_2 = A, B$, the likelihood function, based on allocation and responses up to the nth patient, is given by

$$c(n) \prod_{i=1}^{n} \prod_{k_1 \neq k_2 = A,B} [f_{k_1,k_2}(Z_i, U_i)]^{\delta(k_1,k_2,i)},$$

where $c(n)$ represents the product of the allocation probabilities up to the outcome of the nth patient, and is independent of the parameters of the response distributions. Hence, the corresponding log-likelihood function, ignoring additive constant, is given by

$$\begin{aligned} L_n(\boldsymbol{\theta}) = \frac{-1}{2\sigma^2(1-\rho^2)} \sum_{i=1}^{n} \sum_{k_1 \neq k_2 = A,B} \delta(k_1, k_2, i) \big[& (Z_i - \mu_{k_1})^2 \\ & - 2\rho(Z_i - \mu_{k_1})(U_i - \mu_{k_2} - \phi_{k_1}) \\ & + (U_i - \mu_{k_2} - \phi_{k_1})^2 \big] - n \log\big(2\pi\sigma^2\sqrt{1-\rho^2}\big). \end{aligned}$$

Consequently, the likelihood equations,

$$\frac{\partial L_n(\boldsymbol{\theta})}{\partial \mu_k} = 0 \quad \text{and} \quad \frac{\partial L_n(\boldsymbol{\theta})}{\partial \phi_k} = 0, \quad k = A, B,$$

yield

$$\begin{aligned} & \sum_{i=1}^{n} \delta(A, B, i) \big[-(Z_i - \mu_A) + \rho(U_i - \mu_B - \phi_A) \big] \\ & \quad = \sum_{i=1}^{n} \delta(B, A, i) \big[\rho(Z_i - \mu_B) - (U_i - \mu_A - \phi_B) \big], \end{aligned} \tag{2.1}$$

$$\begin{aligned} & \sum_{i=1}^{n} \delta(B, A, i) \big[-(Z_i - \mu_B) + \rho(U_i - \mu_A - \phi_B) \big] \\ & \quad = \sum_{i=1}^{n} \delta(A, B, i) \big[\rho(Z_i - \mu_A) - (U_i - \mu_B - \phi_A) \big], \end{aligned} \tag{2.2}$$

$$\sum_{i=1}^{n} \delta(A, B, i) \rho(Z_i - \mu_A) - (U_i - \mu_B - \phi_A) = 0 \tag{2.3}$$

and

$$\sum_{i=1}^{n} \delta(B, A, i) \rho(Z_i - \mu_B) - (U_i - \mu_A - \phi_B) = 0. \tag{2.4}$$

Using (2.3) and (2.4) in (2.1), we get

$$\big(1 - \rho^2\big) \sum_{i=1}^{n} \delta(A, B, i) \rho(Z_i - \mu_A) = 0,$$

which implies

$$\hat{\mu}_A = \frac{\sum_{i=1}^{n} \delta(A, B, i) Z_i}{\sum_{i=1}^{n} \delta(A, B, i)}.$$

Similar use of (2.3) and (2.4) in (2.2) yields

$$\hat{\mu}_B = \frac{\sum_{i=1}^{n} \delta(B, A, i) Z_i}{\sum_{i=1}^{n} \delta(B, A, i)}.$$

Next, using $\hat{\mu}_A$ and $\hat{\mu}_B$ in (2.3) and (2.4), we get

$$\widehat{\phi}_A = \frac{\sum_{i=1}^{n} \delta(A, B, i)(U_i - \widehat{\mu}_B)}{\sum_{i=1}^{n} \delta(A, B, i)}, \qquad \widehat{\phi}_B = \frac{\sum_{i=1}^{n} \delta(B, A, i)(U_i - \widehat{\mu}_A)}{\sum_{i=1}^{n} \delta(B, A, i)}.$$

Finally, the likelihood equations $\frac{\partial L_n(\boldsymbol{\theta})}{\partial \sigma^2} = 0$ and $\frac{\partial L_n(\boldsymbol{\theta})}{\partial \rho} = 0$ yield

$$\widehat{\sigma}^2 = \frac{\sum_{i=1}^{n} \sum_{k_1 \neq k_2 = A, B} \delta(k_1, k_2, i)[(Z_i - \widehat{\mu}_{k_1})^2 + (U_i - \widehat{\mu}_{k_2} - \widehat{\phi}_{k_1})^2]}{2n},$$

$$\widehat{\rho} = \frac{1}{n\widehat{\sigma}^2}\Bigg[\sum_{i=1}^{n} \delta(A, B, i)(Z_i - \widehat{\mu}_A)(U_i - \widehat{\mu}_B - \widehat{\phi}_A) + \sum_{i=1}^{n} \delta(B, A, i)(Z_i - \widehat{\mu}_B)(U_i - \widehat{\mu}_A - \widehat{\phi}_B)\Bigg].$$

Then, writing $\widehat{\boldsymbol{\theta}} = (\widehat{\mu}_A, \widehat{\mu}_B, \widehat{\phi}_A, \widehat{\phi}_B, \widehat{\sigma}, \widehat{\rho})$ as an estimate of $\boldsymbol{\theta}$ based on the observations in periods 1 and 2, we get

$$\widehat{\pi} = \Phi\Bigg(\frac{(\widehat{\mu}_A - \widehat{\mu}_B) + \frac{1}{2}(\widehat{\phi}_B - \widehat{\phi}_A)}{\sqrt{\widehat{\sigma}^2(1 - \widehat{\rho})}}\Bigg).$$

Next, corresponding to the ith entering patient in period 3, we define a pair of variables (τ_{Ai}, V_i), where $\tau_{Ai} = 1 - \tau_{Bi} = 1$ or 0 as the ith patient receives treatment A or B and $V_i = \delta(A, B, i)\tau_{Ai}X_{ABAi} + \delta(A, B, i)\tau_{Bi}X_{ABBi} + \delta(B, A, i)\tau_{Ai}X_{BAAi} + \delta(B, A, i)\tau_{Bi}X_{BABi}$. Then, our rule is defined by the following allocation probability

$$P(\tau_{Ai} = 1 \mid \mathcal{D}_n) = \widehat{\pi},$$

where $\mathcal{D}_n = \{\delta(k_1, k_2, i), Z_i, U_i, 1 \leq i \leq n, k_1 \neq k_2, k_1, k_2, k_3 = A, B\}$ represents the data obtained from the first two periods crossover trial. That means, for each entering patient in period 3, a Bernoulli trial is performed with probability of success $\widehat{\pi}$ and the patient receives treatment A or B as the success or failure occurs. We now provide the following results (without proof) as these are useful for any adaptive design.

Result 1. If $\widehat{\boldsymbol{\theta}}_n$ denotes the ML estimate of $\boldsymbol{\theta}$ based on the data obtained from the first two periods, then $\widehat{\boldsymbol{\theta}}_n$ converges to $\boldsymbol{\theta}$ almost surely.

Note. As a consequence of the above result, it follows that $\widehat{\pi}$ converges almost surely to π as n approaches to ∞.

Result 2. As $n \to \infty$, almost surely,

$$\frac{1}{n}\sum_{i=1}^{n} \tau_{Ai} \to \pi.$$

Note. If $N_{k_1k_2k_3}$ represents the number of patients allocated to the treatment sequence $\{k_1k_2k_3\}$, we have

$$N_{k_1k_2k_3} = \sum_{i=1}^{n} \delta(k_1, k_2, i)\tau_{k_3 i}, \quad k_1 \neq k_2; k_1, k_2, k_3 = A, B.$$

As a consequence of the above results, we get

$$\frac{N_{ABA}}{n} \to \frac{1}{2}\pi, \qquad \frac{N_{ABB}}{n} \to \frac{1}{2}(1-\pi),$$
$$\frac{N_{BAA}}{n} \to \frac{1}{2}\pi, \qquad \frac{N_{BAB}}{n} \to \frac{1}{2}(1-\pi)$$

almost surely, as $n \to \infty$.

3 Test for equivalence and related asymptotics

A natural follow up of the proposed rule is to consider some testing problems. At present, for illustration, we consider the testing problem represented by the null hypothesis

$$H_{01} : \text{Treatments A and B are equivalent,}$$

and the alternative hypothesis

$$H_{11} : \text{Treatment A is better than B.}$$

After period 3, for A to be better than B, we have

$$\begin{aligned} & E\left(X_A + X_{BA} + \frac{1}{2}(X_{ABA} + X_{BAA})\right) \\ & > E\left(X_B + X_{AB} + \frac{1}{2}(X_{ABB} + X_{BAB})\right) \\ \Rightarrow \quad & \mu_A + \mu_A + \phi_B + \frac{1}{2}(\mu_A + \phi_B + \mu_A + \phi_A) \\ & > \mu_B + \mu_B + \phi_A + \frac{1}{2}(\mu_B + \phi_A + \mu_B + \phi_B) \\ \Leftrightarrow \quad & (\mu_A - \mu_B) + \frac{1}{3}(\phi_B - \phi_A) > 0. \end{aligned}$$

Unlike a two period two treatment design, we here set the equivalence of A and B by

$$(\mu_A - \mu_B) + \frac{1}{3}(\phi_B - \phi_A) = 0$$

and A to be better than B by

$$(\mu_A - \mu_B) + \frac{1}{3}(\phi_B - \phi_A) > 0.$$

Now, if we set

$$\begin{aligned} S = & \frac{\sum_{i=1}^{n}\delta(A,B,i)Z_i}{N_{AB}} + \frac{\sum_{i=1}^{n}\delta(B,A,i)U_i}{N_{BA}} \\ & + \frac{1}{2}\left[\frac{\sum_{i=1}^{n}\delta(A,B,i)\tau_{Ai}V_i}{N_{ABA}} + \frac{\sum_{i=1}^{n}\delta(B,A,i)\tau_{Ai}V_i}{N_{BAA}}\right] \\ & - \frac{\sum_{i=1}^{n}\delta(B,A,i)Z_i}{N_{BA}} + \frac{\sum_{i=1}^{n}\delta(A,B,i)U_i}{N_{AB}} \\ & + \frac{1}{2}\left[\frac{\sum_{i=1}^{n}\delta(A,B,i)\tau_{Bi}V_i}{N_{ABB}} + \frac{\sum_{i=1}^{n}\delta(B,A,i)\tau_{Bi}V_i}{N_{BAB}}\right], \end{aligned}$$

it is not difficult to show that S approaches almost surely to $3(\mu_A - \mu_B) + (\phi_B - \phi_A)$ as $n \to \infty$. Then, for testing H_{01} against H_{11}, it would be reasonable to use an upper tail test based on the statistic S.

Defining statistics $T_1, T_2, \ldots, T_8$ as

$$T_1 = \sum_{i=1}^{n} \delta(A, B, i)(Z_i - \mu_A), \qquad T_2 = \sum_{i=1}^{n} \delta(B, A, i)(Z_i - \mu_B),$$

$$T_3 = \sum_{i=1}^{n} \delta(A, B, i)(U_i - \mu_B - \phi_A), \qquad T_4 = \sum_{i=1}^{n} \delta(B, A, i)(U_i - \mu_A - \phi_B),$$

$$T_5 = \sum_{i=1}^{n} \delta(A, B, i)\tau_{Ai}(V_i - \mu_A - \phi_B),$$

$$T_6 = \sum_{i=1}^{n} \delta(A, B, i)\tau_{Bi}(V_i - \mu_B - \phi_B),$$

$$T_7 = \sum_{i=1}^{n} \delta(B, A, i)\tau_{Ai}(V_i - \mu_A - \phi_A),$$

$$T_8 = \sum_{i=1}^{n} \delta(B, A, i)\tau_{Bi}(V_i - \mu_B - \phi_A),$$

and using H_{01}, we get

$$S = \left[\frac{T_1}{N_{AB}} + \frac{T_4}{N_{BA}} - \frac{T_2}{N_{BA}} - \frac{T_3}{N_{AB}}\right] + \frac{1}{2}\left[\frac{T_5}{N_{ABA}} + \frac{T_7}{N_{BAA}} - \frac{T_6}{N_{ABB}} - \frac{T_8}{N_{BAB}}\right],$$

after some routine algebraic manipulations. Note that, as the exact null distribution of S cannot be obtained algebraically, we carry out our test procedure by using the asymptotic distribution of S that can be obtained from the following result whose proof is given in the Appendix.

Result 3. Let $\mathbf{T}$ be a 8-component vector with elements $T_1, T_2, \ldots, T_8$. Then, as $n \to \infty$,

$$\frac{1}{\sqrt{n}}\mathbf{T} \xrightarrow{\mathcal{D}} N_8(\mathbf{0}, \Sigma), \tag{3.1}$$

where "$\xrightarrow{\mathcal{D}}$" represents convergence in distribution and the non-zero elements $\sigma_{jj'}$ of Σ are given by

$$\sigma_{jj} = \begin{cases} \dfrac{\sigma^2}{2} & \text{for } j = 1, 2, 3, 4, \\ \sigma^2\left[\dfrac{\pi(1-\pi)(1-2\rho^2)}{4} + \dfrac{\rho^2\pi^2}{1+\rho}\right] & \text{for } j = 5, 7, \\ \sigma^2\left[\dfrac{\pi(1-\pi)(1-2\rho^2)}{4} + \dfrac{\rho^2(1-\pi)^2}{1+\rho}\right] & \text{for } j = 6, 8 \end{cases}$$

and

$$\sigma_{jj'} = \begin{cases} \sigma^2\rho & \text{if } (j, j') \in \{(1,3),(2,4)\}, \\ \sigma^2\pi\rho & \text{if } (j, j') \in \{(1,5),(3,5),(2,7),(4,7)\}, \\ \sigma^2(1-\pi)\rho & \text{if } (j, j') \in \{(1,6),(3,6),(2,8),(4,8)\}, \\ \sigma^2 2\pi(1-\pi)\dfrac{\rho^2}{1+\rho} & \text{if } (j, j') \in \{(5,6),(7,8)\}. \end{cases}$$

4 Simulation studies

We carry out a detailed simulation study with 10,000 repetitions for each set of parameter values. We take the total sample size $n = 100$. We vary $\mu_A - \mu_B$, in which we consider three cases: (a) $\phi_A = \phi_B$, (b) $\phi_A - \phi_B = 0.3$, and (c) $\phi_A - \phi_B = -0.3$.

In Figure 1, we present the allocation proportions to the four sequences ABA, ABB, BAA and BAB. For each of the three situations (a)–(c), the solid lines correspond to the allocation proportions of ABA and BAA (which are same), and the dashed lines correspond to the allocation proportions of ABB and BAB (which are also same by our proposed design).

The case for (a), that is, $\phi_A = \phi_B$ is represented by $\circ$. At $\mu_A - \mu_B = 0$ (i.e., when the treatments are equivalent), the allocation proportion to each sequence is 0.25 provided $\phi_A = \phi_B$. Thereafter, as $\mu_A - \mu_B$ increases, the line corresponding to ABA and BAA goes close to the 0.5 mark. The opposite scenario is observed for the line corresponding to ABB and BAB, where the line goes close to the 0 mark.

The case for (b), that is, $\phi_A - \phi_B = 0.3$ is represented by $\triangle$. Here the allocation proportion to the sequences ABA or BAA is less than 0.25 (and hence the allocation proportion to the sequences ABB or BAB is greater than 0.25) when $\mu_A - \mu_B = 0$. However, the allocation proportion to ABA/BAA increases (and that for ABB/BAB decreases) with $\mu_A - \mu_B$. Here allocation proportion for each sequence becomes 0.25 when $\mu_A - \mu_B = 0.15$.

The case for (c), i.e. $\phi_A - \phi_B = -0.3$ is represented by $+$. Here the allocation proportion to the sequences ABA or BAA starts at a point greater than 0.25 and goes on increasing with

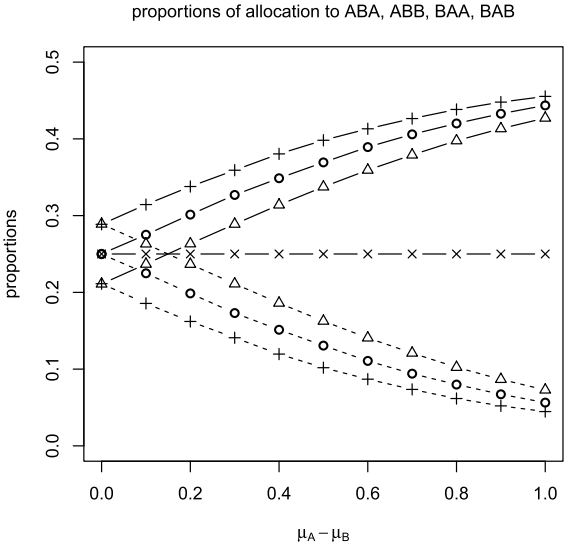

Figure 1 *Allocation proportions to the four sequences ABA, ABB, BAA and BAB. The solid lines corresponds to the allocation proportions of ABA/BAA* (*which are same*), *and the dashed lines corresponds to the allocation proportions of ABB/BAB* (*which are also same*). *Here* $\circ$ *indicates* $\phi_A = \phi_B$; $\triangle$ *indicates* $\phi_A - \phi_B = 0.3$; $+$ *indicates* $\phi_A - \phi_B = -0.3$; $\times$ *indicates equal sample size case.*

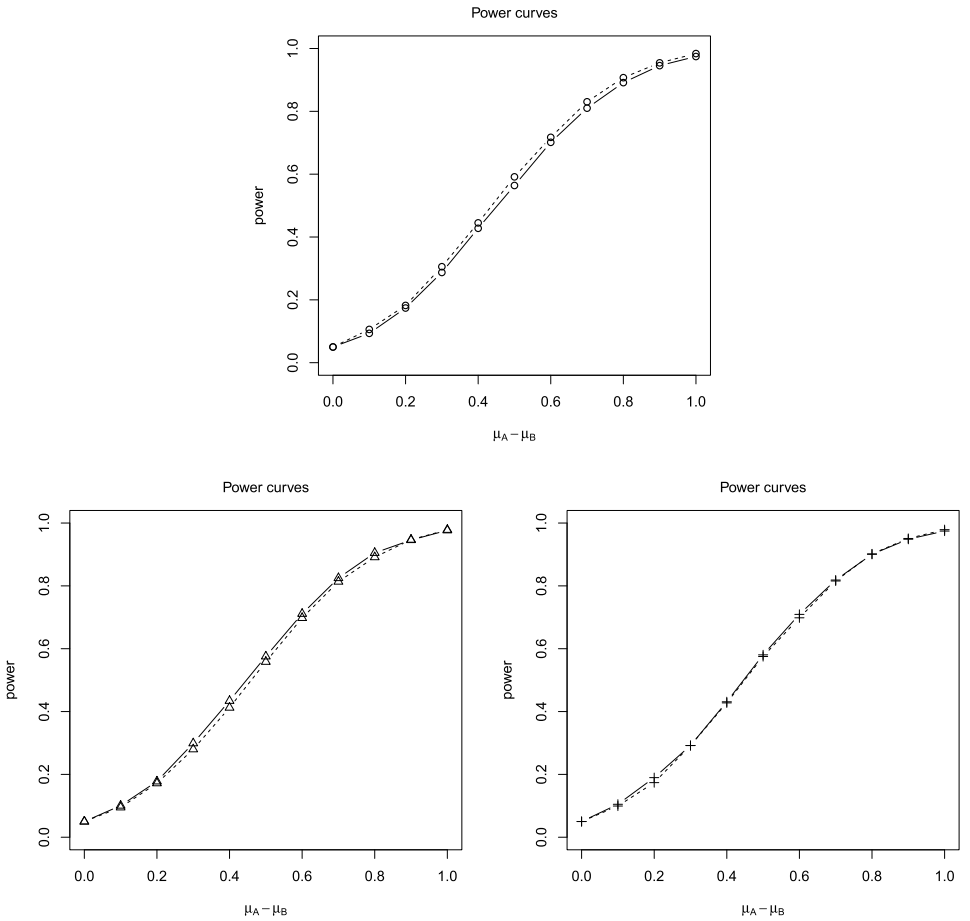

Figure 2 *Power of the test against one-sided alternative, solid lines correspond to the adaptive allocation and dashed lines correspond to the equal allocation. Top row: case for* $\phi_A = \phi_B$; *Bottom left: case for* $\phi_A - \phi_B = 0.3$; *Bottom right: case for* $\phi_A - \phi_B = -0.3$.

$\mu_A - \mu_B$. The opposite scenario happens for the sequences ABB/BAB where it starts with a value less than 0.25 for $\mu_A - \mu_B = 0$ and goes on decreasing with $\mu_A - \mu_B$. Here allocation proportion for each sequence becomes 0.25 when $\mu_A - \mu_B = -0.15$.

The allocation proportion for the all the four sequences remain at the 0.25 mark for the equal allocation case which is represented by $\times$. The departure from this line gives an indication of the gain by our response-adaptive crossover design.

The standard errors of the allocation proportions are low, and are between 0.00030 to 0.00045.

In Figure 2, we represent the power of the test H_{01} against one-sided alternative (H_{11} : $\mu_A - \mu_B + \frac{1}{3}(\phi_B - \phi_A) > 0$) for the adaptive allocation as well as for the equal allocation taking the nominal level (α) at 0.05. The adaptive case is represented by solid line, whereas the equal allocation case is given by dashed line. The case for (a) $\phi_A = \phi_B$ (for both adaptive and equal sample size cases) are represented by $\circ$; the case for (b) $\phi_A - \phi_B = 0.3$ (for both adaptive and equal sample size cases) are represented by $\triangle$; the case for (c) $\phi_A - \phi_B = -0.3$ (for both adaptive and equal sample size cases) are indicated by $+$. We observe that in case (a) the power of the equal allocation case is marginally higher, the difference being never large (keeping empirical levels at 5%). However, in the case (b), the power for the adaptive case is slightly higher (keeping the empirical levels at 5%), whereas in case (c), both the adaptive and equal sample size cases give almost same power (keeping the empirical levels

at 5%). Thus, we conclude that we achieve ethical gain almost without sacrificing power by using our proposed allocation design.

5 Real data analysis

In this section, we illustrate the applicability of the proposed procedure by use of the data set, provided by Matthews (1989), on three-period crossover trial of two antihypertensive agents. This data was analyzed by Ebbutt (1984), Bandyopadhyay, Biswas and Mukherjee (2009, 2012), Bandyopadhyay and Mukherjee (2015), Jones and Kenward (2015), among others. In this data set, treatments A and B are used to represent the two antihypertensive agents. 17 patients are allocated to each of the sequences ABB, BAA, ABA and BAB without any washout periods. The response is the systolic blood pressure of each subject at the end of each period.

We consider |systolic blood pressure $-$ 80| as the new response variables Z_i, U_i and V_i. Using our proposed model, the data provide the estimates of μ_A, μ_B, ϕ_A, ϕ_B, σ^2 and ρ as $\widehat{\mu}_A = 78$, $\widehat{\mu}_B = 67.9545$, $\widehat{\phi}_A = 1.067677$, $\widehat{\phi}_B = -5.477273$, $\widehat{\sigma}^2 = 444.37$ (i.e. $\widehat{\sigma} = 21.08009$), and $\widehat{\rho} = 0.6799437$. The value of the test statistic S comes out to be 24.31844.

Treating the estimates of the parameters as true values, we then carry out a simulation study with 10,000 repetitions where we take $n = 89$, the total sample size in the data (combining the four sequences). We denote the estimates of the parameters obtained from this simulation exercise by $\widehat{\widehat{\mu}}_A, \ldots, \widehat{\widehat{\rho}}$. We observe that the estimates of the parameters come out to be close to the true values in the simulation study, with $\widehat{\widehat{\mu}}_A = 77.9593$ (with s.e. $= 0.0315764$), $\widehat{\widehat{\mu}}_B = 67.9817$ (with s.e. $= 0.03168162$), $\widehat{\widehat{\phi}}_A = 0.9975704$ (s.e. $= 0.04417591$), $\widehat{\widehat{\phi}}_B = -5.386931$ (with s.e. $= 0.04538528$), $\widehat{\widehat{\sigma}} = 21.02954$ (with s.e. $= 0.01372007$), $\widehat{\widehat{\rho}} = 0.6749431$ (with s.e. $= 0.000592441$).

The average sample number (ASN) for the four sequences come out to be $ASN(ABA) = ASN(BAA) = 17.85875$ and $ASN(ABB) = ASN(BAB) = 26.64125$ (with standard errors nearly 0.04).

Although the estimate of μ_A is larger than the estimate of μ_B, the ASN for the sequences ABA and BAA (where the occurrences of A are more than that of B) is lower than that of the sequences ABB and BAB. This is because the estimate of ϕ_A is much larger than that of ϕ_B, and the estimates of ϕ_A and ϕ_B, along with the estimates of μ_A and μ_B, play important role in the allocation for the third period.

Note that, the allocation is skewed in favour of the sequences dominated by treatment B (due to the estimates of the carry-over effects ϕ_A and ϕ_B), and our test procedure is able to catch the significant difference in treatment effects.

The proposed methodology is concerned with some practical restriction. It requires that all patients in the study to complete the first two periods before the time for the third period arrives. The given data example does not satisfy this issue. However, the data example just is redesigning a real situation to illustrate the proposed model and methodology, and hence we ignore this point. However, in practice, such a restriction can be maintained in real crossover trials.

6 Concluding remarks

In the present paper, we studied an adaptive three-period two-treatment crossover trial with normally distributed responses. We specifically stick to the Balaam design, and induced adaptive allocation only at the third period. We can carry out the exercise in a similar fashion with

all the 2^3 treatment sequences $AAA, AAB, \ldots, BBB$ are allowed, and we can induce adaptive allocation in all the three periods. The allocation will be much more skewed in that case. The development is routine following the mechanism used in this paper, and hence is omitted.

As in the test for H_{01} against H_{11}, one may wish to carry out a test for $H_0 : \mu_A = \mu_B$ against $H_1 : \mu_A > \mu_B$. Here, as in the case of S, we can find the statistic

$$S^* = \left[\frac{T_1}{N_{AB}} + \frac{T_4}{N_{BA}} + \frac{T_5}{N_{ABA}} + \frac{T_6}{N_{ABB}}\right] - \left[\frac{T_2}{N_{BA}} + \frac{T_3}{N_{AB}} + \frac{T_7}{N_{BAA}} + \frac{T_8}{N_{BAB}}\right],$$

which approaches almost surely to $2(\mu_A - \mu_B)$ as $n \to \infty$. Hence, an upper tail test based on S^* would be appropriate for testing H_0 against H_1. Similar to S, as the exact null distribution of S^* cannot be obtained algebraically, the asymptotic distribution of S^* can be obtained. Also one may wish to carry out the likelihood ratio test instead of the ad-hoc test procedure suggested in the present paper. But there is no closed form expression of the test statistic in that case, and hence we skip the details.

Appendix

Proof of Result 3. For any fixed constants $c_1, c_2, \ldots, c_8$, writing

$$\begin{aligned}
W_{ni} = {} & \frac{c_1}{\sqrt{n}}\delta(A,B,i)(Z_i - \mu_A) + \frac{c_2}{\sqrt{n}}\delta(B,A,i)(Z_i - \mu_B) \\
& + \frac{c_3}{\sqrt{n}}\delta(A,B,i)(U_i - \mu_B - \phi_A) \\
& + \frac{c_4}{\sqrt{n}}\delta(B,A,i)(U_i - \mu_A - \phi_B) + \frac{c_5}{\sqrt{n}}\delta(A,B,i)\tau_{Ai}(V_i - \mu_A - \phi_B) \\
& + \frac{c_6}{\sqrt{n}}\delta(A,B,i)\tau_{Bi}(V_i - \mu_B - \phi_B) \\
& + \frac{c_7}{\sqrt{n}}\delta(B,A,i)\tau_{Ai}(V_i - \mu_A - \phi_A) + \frac{c_8}{\sqrt{n}}\delta(B,A,i)\tau_{Bi}(V_i - \mu_B - \phi_A),
\end{aligned}$$

we provide the limiting distribution of

$$W_n = \sum_{i=1}^{n} W_{ni}.$$

Next, given $\{\delta(A,B,i), \delta(B,A,i), Z_i, U_i,\ i = 1,2,\ldots,n\}$, the asymptotic distribution of W_n is normal with mean

$$\begin{aligned}
\widehat{\mu}_{cn} = {} & \frac{c_1}{\sqrt{n}}\sum_{i=1}^{n}\delta(A,B,i)(Z_i - \mu_A) + \frac{c_2}{\sqrt{n}}\sum_{i=1}^{n}\delta(B,A,i)(Z_i - \mu_B) \\
& + \frac{c_3}{\sqrt{n}}\sum_{i=1}^{n}\delta(A,B,i)(U_i - \mu_B - \phi_A) \\
& + \frac{c_4}{\sqrt{n}}\sum_{i=1}^{n}\delta(B,A,i)(U_i - \mu_A - \phi_B) \\
& + \widehat{\pi}\frac{c_5}{\sqrt{n}}\sum_{i=1}^{n}\delta(A,B,i)\left[\frac{\rho}{1+\rho}(Z_i - \mu_A) + \frac{\rho}{1+\rho}(V_i - \mu_B - \phi_A)\right]
\end{aligned}$$

$$+(1-\widehat{\pi})\frac{c_6}{\sqrt{n}}\sum_{i=1}^{n}\delta(A,B,i)\tau_{Bi}\Big[\frac{\rho}{1+\rho}(Z_i-\mu_A)$$

$$+\frac{\rho}{1+\rho}(V_i-\mu_B-\phi_A)\Big]$$

$$+\widehat{\pi}\frac{c_7}{\sqrt{n}}\sum_{i=1}^{n}\delta(B,A,i)\tau_{Ai}\Big[\frac{\rho}{1+\rho}(Z_i-\mu_B)+\frac{\rho}{1+\rho}(V_i-\mu_A-\phi_B)\Big]$$

$$+(1-\widehat{\pi})\frac{c_8}{\sqrt{n}}\sum_{i=1}^{n}\delta(B,A,i)\tau_{Bi}\Big[\frac{\rho}{1+\rho}(Z_i-\mu_B)$$

$$+\frac{\rho}{1+\rho}(V_i-\mu_A-\phi_B)\Big],$$

and variance

$$\widehat{\sigma}_{cn}^2=\widehat{\pi}(1-\widehat{\pi})\sigma^2(1-2\rho^2)\frac{1}{n}[N_{AB}(c_5^2+c_6^2)+N_{BA}(c_7^2+c_8^2)],$$

which converges to $\sigma_c^2=\frac{\sigma^2}{4}\pi(1-\pi)(1-2\rho^2)(c_5^2+c_6^2)+c_7^2+c_8^2)$ in probability. Moreover, the asymptotic distribution of $\widehat{\mu}_{cn}$ is normal with zero mean and variance

$$b^2=\frac{\sigma^2}{2}(c_1^2+c_2^2+c_3^2+c_4^2)+\frac{\sigma^2\rho^2\pi^2}{1+\rho}(c_5^2+c_7^2)\frac{\sigma^2\rho^2(1-\pi)^2}{1+\rho}(c_6^2+c_8^2)$$

$$+\sigma^2\rho(c_1c_3+c_2c_4)$$

$$+\sigma^2\pi\rho(c_1c_5+c_3c_5+c_2c_7+c_4c_7)$$

$$+\sigma^2(1-\pi)\rho(c_1c_6+c_3c_6+c_2c_8+c_4c_8)$$

$$+\frac{2\sigma^2\pi(1-\pi)\rho^2}{1+\rho}(c_5c_6+c_7c_8).$$

Hence, as in Hajek and Sidak (1967, Ch. V, pp. 194–195), combining all the above we conclude that the asymptotic distribution of W_n is normal with mean zero and variance $\eta^2=\sigma_c^2+b^2$. Finally, the required result then follows by using the Cramer–Wold device. □

Acknowledgments

The authors wish to thank the Editor, Associate Editor and a reviewer for their careful reading and constructive suggestions which led to an improved version of the paper.

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