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FIVE- PERIODS CROSS-OVER DESIGNS

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ARTICLE INFO	ABSTRACT
	In higher order five period cross-over designs with two treatments, thirty two possible treatment sequences can result; AAAAA, BAAAA, ABAAA, AABAA, AAABA, AAAAB, BBAAA, BABAA,BAABA, BAAAB, ABBAA, ABABA, ABAAB, AABBA, AABAB, AAABB and their duals. Higher-order cross-over designs allow; estimation of treatment effects even in the presence of carry-over effects, provide estimates of intra-subject variability, and draw inference on the carry-over effects. This paper considers four designs; Design 1: BABAA and its dual, design 2: BAABA and its dual, design 3: BABAA, ABABB, BAABA, ABBAB, and design 4: BAAAB, ABBBA, ABBAA, BAABB. The methods for estimating direct treatment effects and treatment carry-over effects are outlined using best linear unbiased estimation method (BLUE), where atraditional modelthat specifies a first order carry-over effect is assumed.

INTRODUCTION

A cross-over design is a repeated measurements design such that each experimental unit receives different treatments during the different time periods. In cross-over designs, a direct treatment effect is the effect of treatment at the time of its application, while a carry-over treatment effect is the effect of a treatment that persist after the end of a treatment period. Carry-over effects appear when the response to a current treatment is affected by the treatment that was applied in the previous period. Cross-over designs are popular for comparing several non-curative treatments for their efficacy. The use of cross-over designs to compare the efficacy of two or more treatments has the advantage that each individual is used as its own control (Jones & Kenward, 2015).Additionally, a cross-over trial has the advantage that fewer participants are needed than the equivalent parallel group trial, and, from a clinical point of view, the experimental treatments are tested within each subject which eliminates many of the confounding factors that might occur in studies with a different design(Godolphin & Godolphin, 2019). For convenience, a cross-over design with t treatments,p periods and s sequences is denoted as C (t, p, s) (Reed III, 2011a). The most common cross-over design that has been widely studied is the two-treatments, two-periods and two sequence cross-over design(C(2, 2, 2))(Baalam, 1968). Designs that have two treatments and two periods were frequently utilized by researchers, but it has been shown that these designs lack the structure to test for carry-over and also produce biased direct treatment effects under the presence of carry-over effects(Hills & Armittage, 1979; Reed III, 2011b). Critiques of the C(2,2,2) with sequences AB and BA allude that the carry-over effects is confounded with sequence by period effects leading to erroneous analyses(Reed, 2012). The carry-over effects may arise for a variety of reasons: an inadequate washout period, a change in physiological or psychological state of the patients caused by the treatment in the first period, or if the treatment effect depends on the mean levels (Hills & Armittage, 1979).

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Potential solutions to these problems have been considered, but these designs are not normally recommended in practice(Fleiss, 1989).Two strategies can be used to obtain higher order cross-over designs which are used to overcome the problems inherent in the C (2, 2, 2) design. The first one is to extend the number of sequences such as Baalam's C (2, 2, 4) design(Baalam, 1968). Secondly, the design can be extended by adding a third period or more and repeating one of the two treatments(Mathews, 1994). In this regard, higher order designs that involve more than two periods are preferable and are becoming more widely used in practice(Godolphin & Godolphin, 2019). In higher order five period cross-over designs with two treatments, thirty two possible treatment sequences can result;AAAAA, BAAAA, ABAAA, AABAA, AAABA, AAAAB, BBAAA, BABAA,BAABA, BAAAB, ABBAA, ABABA, ABAAB, AABBA, AABAB, AAABB and their duals. This paper considers four designs; Design 1: BABAA and its dual, design 2: BAABA and its dual, design 3: BABAA, ABABB, BAABA, ABBAB, and design 4: BAAAB, ABBBA, ABBAA, BAABB. It outlines the BLUE method of estimating direct treatments and first order carry-over effects in the set of five period designs, assuming a traditional model that specifies first order carry-over effect. The unbiased estimates of treatment and carry-over effects are formulated using a strategy outlined by (Mathews, 1994; Laska, Meisner & Kushner, 1993 and Reed, 2010). Assume that the primary goal is to compare two treatments A and B used in a study. By estimating the treatment contrasts $\tau_A - \tau_B$ and period effects π_1 and π_2; first order carry-over effects λ_A , λ_B and μ are regarded as nuisance parameters. Also assume that the response variable is continuous and that there is one response from each subject in each period. Finally, it is assumed that each treatment has simple first order carry-over effect that does not interact with direct effect of the treatment in the subsequent period. This model then assumes the following for the response of individual y_{ij}.

If y_{ijk} denotes the observed response of subject $j(j = 1,2, ... , n)$ in period $i(i = 1, ... , p)$,

Then,

$$y_{ijk} = \mu + \pi_i + \tau_{d(ij)} + \lambda_{d(i-1),j} + \beta_j + e_{ij}, \qquad\qquad (1)$$

Where π_i the effect of period 1 is, $\tau_{d(ij)}$ is the effect of treatment A, $\lambda_{d(i-1,j)}$ is the simple first order carry-over effect of treatment A. It is assumed that all effects are fixed effects. β_j is the effect of patient j and e_{ij} is the error term. The random subject effectβ_j, and the experimental error,e_{ij} are assumed to be mutually independently distributed as N $(0, \sigma^2)$.

2.0 The Best Linear Unbiased Estimation Method for Estimating Treatment and Residual Effects

Consider the estimation of contrasts among direct and residual treatment effects under (1) let

$\tau_A - \tau_B$, and $\lambda_A - \lambda_B$ be the direct treatment effects and carry-over effects to be estimated,theirbest linear unbiased estimators can be written as linear combinations of cell means; for example,

$\tau_A - \tau_B$, $=\sum\sum a_{ij} \overline{y}_{ij}$ and$\lambda_A - \lambda_B$, $=\sum\sum b_{ij} \overline{y}_{ij}$. The estimabilityof$\tau_A - \tau_B$ and$\lambda_A - \lambda_B$ ensures that $\sum_{i=1}^{p} a_{ij}$ and $\sum_{i=1}^{p} b_{ij} = 0$, for$j = 1, ... , s$.

3.0 The designs

3.1 Design 1: BABAA and its Dual

In sequence BABAA, the contrast $c_1 = y_{11} - y_{12} - y_{13} + y_{14} + y_{15}$ has expectation $\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + 2\tau_A$. In sequence ABABB, the contrast $c_2 = y_{21} - y_{22} - y_{23} + y_{24} + y_{25}$ has expectation $\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B$. The difference between contrast C_1 and C_2 forms an unbiased estimator of $(\tau_A - \tau_B)$. For the construction of an unbiased estimator of the carry-over effect $\lambda_A - \lambda_B$, consider $C_3 = y_{11} - 2y_{12} - y_{13} + y_{14} + y_{15}$ and$c_4 = y_{21} - 2y_{22} - y_{23} + y_{24} + y_{25}$ whose expectation are given by; $(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B$ and$(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B$ respectively. The difference between c_3 and c_4 forms an unbiased estimate of$\lambda_A - \lambda_B$.

Table 1. Expected values for C ($2\times 5 \times 2$) Design 1

SEQ	P1	P2	P3	P4	P5
B A B A A	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
A B A B B	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$

Expected values in estimating treatment effects for sequences:

BABAA: $E(C_1) = E(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_A$

ABABB: $E(C_2) = E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B$

BABAA: $E(C_1) = E(Y_{11} - 2Y_{12} - Y_{13} + Y_{14} + Y_{15}) = (\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B$

ABABB: $E(C_2) = E(Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25}) = (\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_A$

Design 2: BABAA and its Dual

In sequence BABAA, the contrast $c_1 = \frac{1}{3}(y_{11} - y_{12} + y_{13} - y_{14} + y_{15})$ has expectation $\frac{1}{3}(\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A.)$ In sequence ABBAB, the contrast $c_2 = \frac{1}{3}(y_{21} - y_{22} + y_{23} - y_{24} + y_{25})$ has expectation $\frac{1}{3}(\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B.)$ The difference between contrast C_1 and C_2 forms an unbiased estimator of $(\tau_A - \tau_B)$. For the construction of an unbiased estimator of the carry-over effect $\lambda_A - \lambda_B$, consider $C_3 = y_{11} + y_{12} + y_{13} - y_{14} - y_{15}$ and $c_4 = y_{21} + y_{22} + y_{23} - y_{24} - y_{25}$ whose expectation are given by; $\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_B$ and $\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_A$ respectively. The difference between c_3 and c_4 forms an unbiased estimate of $\lambda_A - \lambda_B$.

Table 2. Expected values for C ($2 \times 5 \times 2$) Design 2

SEQ	P1	P2	P3	P4	P5
BAABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
ABBAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

Expected values in estimating treatment effects for sequences:

BAABA: $E(C_1) = \frac{1}{3}E(Y_{11} - Y_{12} + Y_{13} - Y_{14} + Y_{15}) = \frac{1}{3}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A]$

ABBAB: $E(C_2) = \frac{1}{3}E(Y_{21} - Y_{22} + Y_{23} - Y_{24} + Y_{25}) = \frac{1}{3}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B]$

Expected values in estimating carry-over effects for sequences:

BAABA: $E(C_1) = E(Y_{11} + Y_{12} + Y_{13} - Y_{14} - Y_{15}) = \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_B$ and

ABBAB: $E(C_2) = E(Y_{21} + Y_{22} + Y_{23} - Y_{24} - Y_{25}) = \mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_A.$

Design 3: BABAA, BAABA and their duals

In sequence BABAA, the expected value of its contrast $c_1 = \frac{1}{4}(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15})$ is given by $\frac{1}{4}[\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_A]$ while it's dual of sequence ABABB of contrast $c_2 = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25})$ has an expected value of $\frac{1}{4}[\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B]$. Similarly, sequence BAABA with contrast $c_3 = \frac{1}{12}(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35})$ has an expected value of $\frac{1}{12}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A]$ whereas it's dual of sequence ABBAB with contrast $c_4 = \frac{1}{12}(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45})$ has an expected value of $\frac{1}{12}[\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B]$. The linear combination of $(c_1 - c_2) + (c_3 - c_4)$ forms an unbiased estimate of the treatment effect $\tau_A - \tau_B$.

In sequence BABAA, the expected value of its contrast $c_1 = \frac{1}{2}[(Y_{11} - 2Y_{12} - Y_{13} + Y_{14} + Y_{15})]$ is given by $\frac{1}{2}[(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B]$ while it's dual of sequence ABABB of contrast $c_2 = \frac{1}{2}[(Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25})]$ has an expected value of $\frac{1}{2}[(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_A]$. Similarly, sequence BAABA with contrast $c_3 = \frac{1}{2}[(Y_{31} + Y_{32} + Y_{33} - Y_{34} - Y_{35})]$ has an expected value of $\frac{1}{2}[\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_B]$ whereas it's dual of sequence ABBAB with contrast $c_4 = \frac{1}{2}E[(Y_{41} + Y_{42} + Y_{43} - Y_{44} - Y_{45})]$ has an expected value of $\frac{1}{2}[\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_A]$. The linear combination of $(c_1 - c_2) + (c_3 - c_4)$ forms an unbiased estimate of the treatment effect $\lambda_A - \lambda_B$.

Table 3. Expected values for C ($2 \times 5 \times 4$) Design 3

SEQ	P1	P2	P3	P4	P5
BABAA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_B + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
ABABB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_A + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$
BA ABA	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_A + \lambda_B$
ABBAB	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_2 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_B + \lambda_A$

Expected values in estimating treatment effects for sequences:

BABAA: $E(c_1) = \frac{1}{4}E(Y_{11} - Y_{12} - Y_{13} + Y_{14} + Y_{15}) = \frac{1}{4}[\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_A]$

ABABB: $E(c_2) = \frac{1}{4}E(Y_{21} - Y_{22} - Y_{23} + Y_{24} + Y_{25}) = \frac{1}{4}[\mu + (\pi_1 - \pi_2 - \pi_3 + \pi_4 + \pi_5) + \tau_B]$

BAABA: $E(c_3) = \frac{1}{12} E(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}) = \frac{1}{12} [\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_A]$

ABBAB: $E(c_4) = \frac{1}{12} E(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}) = \frac{1}{12} [\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + 3\tau_B]$

Expected values in estimating carry-over effects for sequences

BABAA: $E(c_1) = \frac{1}{2} E [(Y_{11} - 2Y_{12} - Y_{13} + Y_{14} + Y_{15})] = \frac{1}{2} [(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_B]$

ABABB: $E(c_2) = \frac{1}{2} E[(Y_{21} - 2Y_{22} - Y_{23} + Y_{24} + Y_{25})] = \frac{1}{2} [(\pi_1 - 2\pi_2 - \pi_3 + \pi_4 + \pi_5) - \lambda_A]$

BAABA: $E(c_3) = \frac{1}{2} E[(Y_{31} + Y_{32} + Y_{33} - Y_{34} - Y_{35})] = \frac{1}{2} [\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_B$

ABBAB: $E(c_4) = \frac{1}{2} E[(Y_{41} + Y_{42} + Y_{43} - Y_{44} - Y_{45})] = \frac{1}{2} [\mu + (\pi_1 + \pi_2 + \pi_3 - \pi_4 - 2\pi_5) - \lambda_A]$

Design 4: BAAAB, ABBAA and their duals

In sequence BAAAB, the expected value of its contrast $c_1 = \frac{1}{2}(-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15})$ is given by $\frac{1}{2} [-\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)]$ while it's dual of sequence ABBBA of contrast $c_2 = \frac{1}{2}(-Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25})$ has an expected value of $\frac{1}{2} [-\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)]$. Similarly, sequence ABBAA with contrast $c_3 = \frac{1}{2}(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35})$ has an expected value of $\frac{1}{2} [\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_A)]$, whereas it's dual of sequence BAABB with contrast $c_4 = \frac{1}{2}(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45})$ has an expected value of $\frac{1}{2} [\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_B)]$. The linear combination of $(c_1 - c_2) + (c_3 - c_4)$ forms an unbiased estimate of the treatment effect $\tau_A - \tau_B$. In sequence BAAAB, the expected value of its contrast $c_1 = \frac{1}{6}[(Y_{11} - 2Y_{12} + Y_{13} + Y_{14} - Y_{15})]$ is given by $\frac{1}{6}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_B + \lambda_A]$, while it's dual of sequence ABBBA of contrast $c_2 = \frac{1}{6} [(Y_{21} - 2Y_{22} + Y_{23} + Y_{24} - Y_{25})]$ has an expected value of $\frac{1}{6}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_A + \lambda_B]$. Similarly, sequence ABBAA with contrast $c_3 = \frac{1}{6}[(Y_{31} + Y_{32} + Y_{33} - 2Y_{34} + Y_{35})]$ has an expected value of $\frac{1}{6}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_B + 2\lambda_A]$ whereas it's dual of sequence BAABB with contrast $c_4 = \frac{1}{6} [(Y_{41} + Y_{42} + Y_{43} - 2Y_{44} + Y_{45})]$ has an expected value of $\frac{1}{6}[2\mu + (\pi_1 + \pi_2 - \pi_3 + 2\pi_4 + \pi_5) - \lambda_A + 2\lambda_B]$. The linear combination of $(c_1 - c_2) + (c_3 - c_4)$ forms an unbiased estimate of the treatment effect $\lambda_A - \lambda_B$.

Table 4. Expected values of C ($2 \times 5 \times 4$) Design 4

SEQ	P1	P2	P3	P4	P5
BAAAB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_3 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_A + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_A$
ABBBA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_B + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_B$
ABBAA	$\mu + \pi_1 + \tau_A$	$\mu + \pi_2 + \tau_B + \lambda_A$	$\mu + \pi_3 + \tau_B + \lambda_B$	$\mu + \pi_4 + \tau_A + \lambda_B$	$\mu + \pi_5 + \tau_A + \lambda_A$
BAABB	$\mu + \pi_1 + \tau_B$	$\mu + \pi_2 + \tau_A + \lambda_B$	$\mu + \pi_2 + \tau_A + \lambda_A$	$\mu + \pi_4 + \tau_B + \lambda_A$	$\mu + \pi_5 + \tau_B + \lambda_B$

Expected values in estimating treatment effects for sequences:

BAAAB: $E(c_1) = \frac{1}{2} E(-Y_{11} - Y_{12} - Y_{13} + Y_{14} - Y_{15}) = \frac{1}{2} [-\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_B + \tau_A) - (\lambda_A + \lambda_B)]$

ABBBA: $E(c_2) = \frac{1}{2} E(-Y_{21} - Y_{22} - Y_{23} + Y_{24} - Y_{25}) = \frac{1}{2} [-\mu + (-\pi_1 - \pi_2 - \pi_3 + \pi_4 - \pi_5) - (2\tau_A + \tau_B) - (\lambda_A + \lambda_B)]$

ABBAA: $E(c_3) = \frac{1}{2} E(Y_{31} - Y_{32} + Y_{33} - Y_{34} + Y_{35}) = \frac{1}{2} [\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_A)]$

BAABB: $E(c_4) = \frac{1}{2} E(Y_{41} - Y_{42} + Y_{43} - Y_{44} + Y_{45}) = \frac{1}{2} [\mu + (\pi_1 - \pi_2 + \pi_3 - \pi_4 + \pi_5) + (\tau_B)]$

Expected values in estimating carry-over effects for sequences

BAAAB: $E(c_1) = \frac{1}{6} E[(Y_{11} - 2Y_{12} + Y_{13} + Y_{14} - Y_{15})] = \frac{1}{6}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_B + \lambda_A]$

ABBBA: $E(c_2) = \frac{1}{6} E[(Y_{21} - 2Y_{22} + Y_{23} + Y_{24} - Y_{25})] = \frac{1}{6}[2\mu + (\pi_1 - 2\pi_2 + \pi_3 + \pi_4 - \pi_5) - 2\lambda_A + \lambda_B]$

ABBAA: $E(c_3) = \frac{1}{6} E[(Y_{31} + Y_{32} + Y_{33} - 2Y_{34} + Y_{35})] = \frac{1}{6}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_B + 2\lambda_A]$

BAABB: $E(c_4) = \frac{1}{6} E[(Y_{41} + Y_{42} + Y_{43} - 2Y_{44} + Y_{45})] = \frac{1}{6}[2\mu + (\pi_1 + \pi_2 - \pi_3 - 2\pi_4 + \pi_5) - \lambda_A + 2\lambda_B]$

DISCUSSION

Like other cross-over designs, the C (2, 5) have an advantage that each subject is used as their own control. Additionally, these designs require fewer subjects for the same number of observations than the non-cross-over designs. In this regard, the designs are efficient in situations where the experimental subjects are scarce and are expensive to recruit and maintain in the study.

Moreover, it is possible to estimate important treatment contrasts in these designs even when the carry-over effects are assumed in the overall model. The main problem with clinical trials practitioners who apply cross-over designs is the presence of carry-over effects is that, in any given period, an observation from an experimental unit can be affected not only by the treatment effect in which it is applied, but also by the effect of a treatment applied in the preceding period. One way to avoid the impact of carry-over is to insert a washout period between two successive periods with the aim of eliminating the carry-over effect. The washout periods effectively increases the interval between the observed periods and can help in overcoming the carry-over effect if the carry-over effect is not expected to persist. Alternatively, the design can be designed in such a way that the difference in treatment effects may be estimated after adjusting for the presence of possible carry-over effects. More precise estimates can be achieved if the two approaches can be applied in cross-over designs concurrently, like in this study.

Conclusion

This article considered C (2, 5) designs for a simple one period carry-over effect model. The four designs presented are ideal because the design efficiencies are optimal. Higher order cross-over designs are useful because they allow treatment effects to be estimated even in the presence of carry-over effects and they can provide estimates of intra-subject variability and draw inference on the carry-over effect (chow & Lu, 1992).

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