Robust assessment of two-treatment higher-order cross-over designs against missing values

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Abstract

In scientific experiments where human behaviour or animal response is intrinsically involved, such as clinical trials, there is a strong possibility of recording missing values. Missing data in a clinical trial has the potential to impact severely on study quality and precision of estimates. In studies which use a cross-over design, even a small number of missing values can lead to the eventual design being disconnected. In this case, some or all of the treatment contrasts under test cannot be estimated and the experiment is compromised since little can be achieved from it.

Experiments comparing two treatments that use a cross-over design with more than two experimental periods are considered. Methods to limit the impact of missing data on study results are explored. It is shown that the breakdown number and, if it exists, perpetual connectivity of the planned design are useful robustness properties which guard against the possibility of a disconnected eventual design. A procedure is proposed which assesses planned designs for robustness against missing values and the method is illustrated by assessing several designs that have been previously considered on cross-over studies.

Keywords: Cross-over design, clinical trial, subject drop-out, breakdown number, perpetually connected

1. Introduction

Cross-over designs are a popular choice for clinical trialists, due in part to the additional efficiency gains they provide (Chow and Liu, 2008; Jones and Kenward, 2015; Shih and Aisner, 2015). In a cross-over trial, fewer participants are needed than the equivalent parallel group trial, and, from a clinical viewpoint, the experimental treatments are tested within each subject which eliminates many of the confounding factors that might occur in studies with a different design. In particular, Chow and Liu (2008, page 37), point out that regulatory agencies, such as the U.S. Food and Drug Administration (FDA), look favourably on studies which implement a cross-over design for bioequivalence and bioavailability pharmacology trials. For bioequvialence studies, the cross-over design is the study design recommended by both the FDA and the European Medicines Agency (EMA, 2010; FDA, 2001).

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 (Freeman, 1989; Hills and Armitage, 1979). Potential solutions to these problems have also been considered, but these designs are not normally recommended in practice (Fleiss, 1989; Senn, 2001). Therefore, higher-order designs that involve two treatments administered over more than two periods are preferable and are becoming more widely used. Such a design repeats any of the two experimental interventions a specific amount of times in a number of sequences. A four period design with four unique sequences is proposed by the FDA as the most suitable design to use for bioequivalence studies with two treatments if carry-over is expected (FDA, 2001). There has been a thorough examination to determine the best two-treatment higher-order design in terms of both statistical

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and cost efficiency (Matthews, 1987; Kunert, 1991; Kushner, 1997; Jones and Kenward, 2015; Reed, 2012; Yuan and Zhou, 2005; Zhou, Yuan, Reynolds et al., 2006).

However, little attention has been paid in the literature to how robust various cross-over designs are to data that becomes unavailable during the course of the experiment. In clinical trials, missing data is not uncommon and many studies experience subject drop-out of up to 30% (National Academy of Sciences, 2010, page 39). Participants can drop-out through administrative issues such as change of location, unhappiness with trial processes or difficulty with attending study visits. It is also not unusual for a number of participants to withdraw consent part-way through the trial. As well as this, subjects may leave the study prematurely for reasons related to treatment, or even be excluded due to protocol deviations, for example poor adherence to the intervention or use of concomitant medication. This issue can be especially prevalent in cross-over studies, as participants experience more treatments and longer follow-up time when compared to the equivalent parallel-group study. Exposure to different interventions could result in a multitude of side effects and/or adverse drug reactions which could lead to subject drop-out at various points in the study. In higher order cross-over studies, this issue is heightened further as the number of experimental and associated washout periods are increased which can lead to trials with lengthy follow-up. Similar difficulties with drop-out during the term of the experiment can also arise when animal subjects are involved in pharmaceutical studies; see for example, Bate et al. (2008).

Missing data in any experiment will result in a loss of precision of parameter contrasts in effects of interest and, in some cases, can lead to a design which is disconnected; see for example Godolphin (2004). In studies which use a cross-over design, a specific pattern of drop-out behaviour can result in a disconnected design in which some and occasionally all contrasts in treatment direct, treatment carry-over and period effects will not be estimable. Such a situation has the potential to compromise the experiment severely, and could result in substantial loss of information about the aims of the study as well as incurring unwanted excess monetary and time costs from a repeated experiment. Throughout this paper, the design that is selected for the experiment is called the *planned design* and the design that remains after any drop-out is referred to as the *eventual design*. It is expected that the analysis of the experiment will be based on the eventual design. A useful measure when planning an experiment to reduce or even prevent the possibility of a disconnected eventual design is the concept of the minimum number of observations that a planned design is required to lose for the corresponding eventual design to be disconnected; this is referred to in what follows as the *breakdown number* of the planned design. Thus, planned designs with a high breakdown number are advantageous on grounds of robustness to missing data.

Contributions to the analysis of cross-over designs when one or more subjects fail to complete all periods of treatment are given by Patel (1985); Shih and Quan (1997); Ho et al. (2012) and references therein. The consideration of robustness properties of cross-over designs with regard to subject drop-out appears to be confined to the class of planned designs which are uniformly balanced repeated measurement designs; see for example Majumdar, Dean and Lewis (2008); Godolphin and Godolphin (2017). This class of designs necessarily excludes from consideration the two-treatment higher-order designs.

In this paper many of the planned two-treatment higher-order cross-over designs are assessed for robustness to missing values due to subject drop-out. By tradition, the two treatments are labelled A and B. A general treatment of connectivity and estimability is given and the approach is illustrated by considering several examples. In particular all possible two-treatment, four-period, four sequence dual cross-over designs are examined and ranked by breakdown number and minimum variance, thus enabling the identification of a good design which is robust against missing observations caused by subject drop-out. A discussion of the findings and how these may implicate designing cross-over experiments is also presented.

2. Preliminaries

2.1. Definitions and Notation

Let a cross-over design D be selected for the experiment and suppose that the $n \times 1$ observation vector Y is a response variable which follows the additive model, described in matrix form as

$$Y = \mu 1_n + X_1\tau + X_2\rho + X_3\alpha + X_4\beta + \varepsilon, \tag{1}$$

where X_1, X_2, X_3 and X_4 are components of the design matrix for the planned design, 1_n is the $n \times 1$ vector, all of whose elements are unity, and ε is a $n \times 1$ random vector with expectation 0_n and covariance matrix $\sigma^2 I_n$ ($\sigma^2 > 0$).

It is assumed that there is one response from each subject in each period and that there is no carry-over effect for a response for any subject in the first period. Here μ is a mean parameter, $\tau = [\tau_A\ \tau_B]', \rho = [\rho_A\ \rho_B]', \alpha, \beta$ are vectors of treatment direct, treatment carry-over, row (period) and column (subject) effects of sizes 2×1, 2×1, $p \times 1$ and $s \times 1$ respectively. It is further assumed that n, the number of observations derived from the planned design D is such that $n \geq p + s + 1$. In most circumstances the main interest in the experiment is the comparison $\tau_A - \tau_B$ of the treatment direct effects whilst the comparison $\rho_A - \rho_B$ of the treatment carry-over effects is often a secondary, but usually nontrivial, interest.

In what follows it is convenient to express the model description (1) in summary form as

$$Y = \mu 1_n + X\theta + \varepsilon, \tag{2}$$

where $X = [X_1\ X_2\ X_3\ X_4]$ and the parameter vector $\theta = [\tau'\ \rho'\ \alpha'\ \beta']'$, so that the design matrix for the planned design D is $X_D = [1_n\ X]$. The linear parameter combinations of interest are mostly, but not exclusively, contrasts in the treatment effects, both direct and carry-over, and contrasts in the period or subject effects and linear combinations of them. However, in no cases are parametric combinations involving μ of interest and these are excluded by adopting the model description (2). Particular concern is for the *estimable space* Λ, i.e. the set of vectors λ of size $(p+s+4)\times 1$ that define the coefficients of estimable parametric combinations

$$\Lambda = \{\lambda : \lambda'\theta \text{ is estimable}\}. \tag{3}$$

The planned design is said to be totally connected, a term due to Srivastava and Anderson (1970), if the independent contrasts $\tau_A - \tau_B$, $\rho_A - \rho_B$ and a further $p + s - 2$ independent parametric combinations in treatment, subject and period effects are estimable. The planned design is totally connected if and only if the dimension of the estimable space is $\dim(\Lambda) = p + s$. A further equivalent condition for total connectivity of D is that the rank of X is given by $\text{rank}(X) = \text{rank}(X_D) = p + s + 1$ (Godolphin, 2013). For simplicity the single term *connected* is used throughout the paper when these equivalent conditions are satisfied.

2.2. Unavailability of data due to subject drop-out

One of the distinguishing features of a cross-over design that is not normally associated with a row-column design in general is that the corresponding experiment will be conducted over a length of time that is divided into p separate measurement periods. It follows that if a subject drops out in the qth period then the number of measurements that are not recorded is $p - q$ which may be substantially larger than unity. This, of course, assumes that a subject who drops out does not return to the study in subsequent periods, which is usually the case. Consequently the number of measurements that are missing may be considerably larger than the number of subjects who leave the study prematurely. Furthermore most of these missing observations will be lost from later periods of the experiment. Although a subject may drop out of the study at any period it is reasonable to suppose that the subject is less likely to do so in the earlier periods, except possibly when there is a reaction to the experimental treatment.

Two suppositions are made in this paper about the unavailability of data due to subject drop-out. Firstly, it is assumed that subject drop-out is missing at random (MAR), which implies that the missingness mechanism depends only on the data that are measured and not on any of the missing observations (Little and Rubin, 2002). When data are MAR it follows that valid estimates of estimable parametric combinations can be obtained using traditional likelihood-based approaches, which ignore the missing data mechanism (Molenberghs and Kenward, 2007, Chapter 12). Thus, situations where data is missing not at random (MNAR), for example where drop-out is due to adverse or favourable reactions to the intervention, are not considered here. In this case, the missingness mechanism also depends on the observations which are missing. A discussion of cross-over studies where data is MNAR is given by Rosenkranz (2014) and Matthews and Henderson (2013).

Secondly, a simplified assumption is made in the paper that each subject remains in the study for at least two periods. This assumption is equivalent to requiring that each subject block has a minimum of two observations which is necessary for the variability within that block to be measurable. Furthermore, this assumption is consistent with the familiar situation that subject drop-out tends to occur in the later periods of the experiment.

2.3. Robustness criteria

It is necessary to formalize methods for categorizing the robustness properties of a design which may be subject to loss of information due to subject drop-out. Given a planned design D, it sometimes happens that the usual analysis of D cannot be carried out because some measurements are not recorded after one or more subjects leave the study prematurely. Instead it is necessary to analyze the eventual design, D_e say, using the measurements which are available. Clearly for a given D there are many possible eventual designs D_e which could occur. We first consider the robustness concept of breakdown number which was introduced in a paper by Mahbub Latif et al. (2009).

Definition 1. The *breakdown number* m_D of a planned design D is the minimum number of missing observations that result in at least one disconnected eventual design.

This definition implies that there is at least one D_e which is disconnected; this design will consist of m_D fewer measurements than would be available from D. Furthermore there will usually be several other disconnected eventual designs which have m_D or more observations missing when compared with the planned design.

When D has breakdown number m_D then no eventual design D_e will be disconnected if fewer than m_D observations are lost during the experiment. Thus D is robust to the unavailability of observations due to subject drop-out if m_D is relatively high. Note, however, that the loss of m_D observations does not mean necessarily that the number of subjects dropping out is high. The extreme case for high breakdown number is a perpetually connected design which was discussed by the authors in a previous paper (Godolphin and Godolphin, 2017).

Definition 2. A planned design is *perpetually connected* if all subjects complete the first two periods and the eventual design is connected irrespective of subject drop-out behaviour in succeeding periods.

Thus D is perpetually connected if there is no D_e which is disconnected, conditional on no drop-out in the first two periods of study. The breakdown number for a perpetually connected design D will be cited as $m_D = \infty$.

2.4. Designs to compare four treatments using eight subjects

The robustness concepts of subsection 2.3 can be illustrated by considering an experiment to compare treatments A and B by using eight subjects over four periods. Here and throughout the paper the columns of the design refer to the subjects and the rows refer to periods in sequential order. Two designs for this study are considered. Design 2.4.1 is given by four replicates of the optimal two-subject four period design, confer Jones and Kenward (2015, page 125), and Design 2.4.2 is given by Hedayat and Stufken (2003, page 525).

A	B	A	B	A	B	A	B
B	A	B	A	B	A	B	A
B	A	B	A	B	A	B	A
A	B	A	B	A	B	A	B

Design 2.4.1. From Jones and Kenward (2015)

A	B	A	B	A	B	A	B
A	B	B	A	B	A	B	A
B	A	A	B	B	A	B	A
A	B	A	B	A	B	B	B

Design 2.4.2. Hedayat-Stufken Design

Each of these two designs has 19 degrees of freedom available for the residual error variance. Each design is robust to the possibility that up to three subjects drop out of the study in the third or fourth period. However the breakdown number for Design 2.4.1 is eight, consequently the experiment based on Design 2.4.1 is at risk if four or more subjects leave prematurely. For example, Design 2.4.3 is the eventual design after four subjects dropped out in the third period, where the symbol '*' signifies a missing observation. Design 2.4.3 is disconnected. No unbiased estimator of the direct treatment contrast $\tau_A - \tau_B$ exists even though twelve replications of treatment A and twelve replications of treatment B have been recorded successfully. Furthermore no unbiased estimator of the carry-over treatment contrast $\rho_A - \rho_B$ exists.

A	B	A	B	A	B	A	B
B	A	B	A	B	A	B	A
$*$	A	$*$	A	$*$	A	$*$	A
$*$	B	$*$	B	$*$	B	$*$	B

Design 2.4.3. Drop-out from Design 2.4.1

The unpleasant outcome described here is avoided with Design 2.4.2. In this case no drop-out activity in the third or fourth periods will result in a disconnected eventual design. This is indicated by specifying the breakdown number $m_D = \infty$. Given the assumption that all subjects remain with the study for two periods then contrasts $\tau_A - \tau_B$ and $\rho_A - \rho_B$ have unbiased estimators, irrespective of subject drop-out behaviour in periods three and four. The Hedayat-Stufken design does not have the risk due to drop-out in the third or fourth periods that is associated with Design 2.4.1.

3. Criteria for cross-over design assessment

3.1. Introductory Comments

Much of the attention on robustness against the unavailability of observations has tended to concentrate on various types of incomplete block designs, following the classic contribution of Ghosh (1982) on balanced incomplete blocks; see Godolphin and Godolphin (2015) and references therein. Some of the criteria developed in these works can apply to the more structured cross-over designs. In this section various robustness criteria are considered to assist with the assessment, selection and subsequent analysis of a two-treatment cross-over design.

3.2. Ranking Designs by Breakdown Number

Searle (1971), page 181, has given the traditional definition of estimability of a parametric combination $\lambda_\mu \mu + \lambda'\theta$, where the mean parameter μ and the parameter vector θ are defined in (2), as follows: $\lambda_\mu \mu + \lambda'\theta$ is estimable if and only if there is a $n \times 1$ vector w such that $[\lambda_\mu \ \lambda'] = w'X_D = w'[1_n \ X]$. Taking $\lambda_\mu = 0$, this becomes

Proposition 1. For the planned design D defined in (2),

$$\lambda'\theta \text{ is estimable if and only if there is } w \text{ such that } \ w'1_n = 0 \ \text{ and } \ \lambda' = w'X. \tag{4}$$

The condition $\lambda' = w'X$ in Proposition 1 is equivalent to requiring $\lambda \in \mathcal{R}_{\text{plan}}$, where $\mathcal{R}_{\text{plan}}$ is the row space of X. Thus the criterion cited by (4) is given in a particularly useful form for dealing with the possibility of missing values since each observation has a one-to-one relationship with a row of X. Consequently the loss of one or more observations from D to give the eventual design D_e is equivalent to losing the corresponding spanning vectors from $\mathcal{R}_{\text{plan}}$ to yield a new space $\mathcal{R} \subseteq \mathcal{R}_{\text{plan}}$. As long as the dimension, $\dim(\mathcal{R})$, of the remaining row space is the same as $\dim(\mathcal{R}_{\text{plan}})$ then $\mathcal{R}$ and $\mathcal{R}_{\text{plan}}$ are the same space. Hence the estimability space for D_e is the same Λ as specified in equation (3), i.e. if D is connected then D_e is a connected design. On the other hand, if $\dim(\mathcal{R}) < \dim(\mathcal{R}_{\text{plan}})$ then $\mathcal{R}$ is a strict subspace of $\mathcal{R}_{\text{plan}}$ so that D_e is disconnected and the corresponding estimability space will also be a strict subspace of Λ. Therefore certain parametric combinations will no longer be estimable. Typically the contrasts $\tau_A - \tau_B$ and $\rho_A - \rho_B$ are inestimable so the experiment will be compromised.

An example of this unwelcome situation is provided when D is given by Design 2.4.1 in Section 2.4; in this case the loss of eight observations to yield Design 2.4.3 corresponds to the loss of eight spanning vectors from $\mathcal{R}_{\text{plan}}$, with dimension $p + s + 1 = 4 + 8 + 1 = 13$, to yield the residual row space $\mathcal{R}$ with lower dimension 12 in which $\tau_A - \tau_B$ and $\rho_A - \rho_B$ and many period and subject contrasts are inestimable. Even if all measurements from Design 2.4.3 are made successfully no unbiased estimators of either $\tau_A - \tau_B$ or $\rho_A - \rho_B$ exists.

The choice of a cross-over design, in general, is typically made on grounds of estimator efficiency. Whilst this is always an important consideration the consequences of having to deal with a disconnected eventual design because of drop-out suggest strongly that robustness properties should also be taken into account. To achieve this it is required to determine a way of ranking designs in terms of robustness properties.

Definition 3. If D_1 and D_2 are cross-over designs with the same dimension then D_1 is said to be *more robust* than D_2 when their breakdown numbers satisfy $m_{D_1} > m_{D_2}$.

It follows that if many designs are under consideration then the design D with breakdown number $\max(m_D)$ is more robust than the competing designs and should be preferred on grounds of robustness. When several designs have the same largest breakdown number $\max(m_D)$ then efficiency considerations should apply to these designs. Evidently a useful preliminary step is to aim to identify those designs that possess this largest breakdown number.

Definition 4. Given a cross-over design D, let $D_{\min}$ denote the eventual design which remains after all s subjects drop-out after completing two periods. Then $D_{\min}$ is termed the *minimal design* associated with D.

Assume without loss of generality that the ordering of the rows of X is such that X_*, the submatrix of X consisting of the first $2s$ rows, corresponds to the first two periods of the design. Then X_* can be written as

$$X_* = [X_{\min} \;\; 0^*_{2s}] \tag{5}$$

where $X_{\min}$ is the minimal design matrix and 0^*_{2s} is a $2s \times (p-2)$ matrix consisting of zero elements. Clearly the rows of X_* form a subspace $\mathcal{R}_* \subseteq \mathcal{R}_{\text{plan}}$. Using an argument of Godolphin and Godolphin (2017), it can be shown that $\dim(\mathcal{R}_*) = \text{rank}(X_{\min})$, consequently there are two possible cases to consider. If the minimal design matrix $X_{\min}$ is connected, i.e. it has maximal rank $s+3$, then the deficiency in the dimension $\dim(\mathcal{R}_*)$ compared to $\dim(\mathcal{R}_{\text{plan}})$ is due solely to the fact that no measurements are made in the final $p-2$ periods which are missing in the minimal design. This implies that no drop-out activity from the design D which occurs in these final $p-2$ periods will result in a disconnected eventual design, i.e. D is perpetually connected. On the other hand if $X_{\min}$ is disconnected then there will be other eventual designs that include $X_{\min}$ which are also disconnected.

3.3. Choosing a Perpetually Connected Design

Clearly if a perpetually connected design exists then it should be considered seriously for selection. However, it sometimes happens that the set $\mathcal{D}$ of perpetually connected designs which are available may contain several members. In these circumstances a choice of planned design from $\mathcal{D}$ is sensible. Considerable attention has been given to design selection based on various optimality criteria which assume no drop-out will arise: see the useful reviews in Jones and Kenward (2015, Chapter 3), and Chow and Liu (2008, Chapters 9-10).

In addition the authors suggest making use of a complementary method of choice between members of $\mathcal{D}$ that does not appear to be available easily in many software packages. This procedure gives the explicit forms for the unbiased estimators of $\tau_A - \tau_B$ and $\rho_A - \rho_B$ as linear forms in the observations Y, for each competing member of $\mathcal{D}$. The method is based on an established alternative test of estimability, described by Searle (1971, Section 5.4). Suppose that $\lambda \in \Lambda$, where Λ is the estimability space defined in (3). Then $\lambda'\theta$ is estimable so it follows from Proposition 1 that there is a w of size $n \times 1$, referred to as the *weight vector*, such that

$$\lambda' = w'X. \tag{6}$$

Let $(X'X)^-$ be a generalized inverse of $X'X$, i.e. $(X'X)^-$ satisfies $X'X(X'X)^-X'X = X'X$. Then $P_X = X(X'X)^-X'$ is the orthogonal projection operator on the column space of X and

$$P_X X = X \Rightarrow X' = X'P_X = X'X(X'X)^-X'$$

after noting that P_X is symmetric. Thus if S_X is defined as $S_X = X'X(X'X)^-$ then $S_X X' = X'$, i.e. S_X is a projection operator on the column space of X', which is $\mathcal{R}_{\text{plan}}$. This implies that $\lambda \in \mathcal{R}_{\text{plan}}$ if and only if $\lambda' S'_X = \lambda'$. From this condition it follows that, whenever $\lambda'\theta$ is estimable

$$\lambda' = \lambda' S'_X = \lambda'(X'X)^-X'X = w'X, \tag{7}$$

taking account of (6), where the weight vector is given by

$$w' = \lambda'(X'X)^-X'. \tag{8}$$

Searle (1971, page 185) remarks that "the derivation of a vector λ satisfying $\lambda' = w'X$ may not always be easy", however the improvement in methods for computing the expression (8) in the intervening years has probably made this comment somewhat pessimistic. In particular, it follows from (8) that expressions for the least-squares estimators of the estimable contrasts $\tau_A - \tau_B$ and $\rho_A - \rho_B$ are given by

$$\widehat{\tau}_A - \widehat{\tau}_B = w'_\tau Y = \lambda'_\tau (X'X)^-X'Y \;\text{ and }\; \widehat{\rho}_A - \widehat{\rho}_B = w'_\rho Y = \lambda'_\rho (X'X)^-X'Y \tag{9}$$

respectively, where λ_τ and λ_ρ are the $(p+s+4) \times 1$ vectors

$$\lambda_\tau = [1 \;\; -1 \; 0 \; 0 \; 0'_{p+s}]' \quad \text{and} \quad \lambda_\rho = [0 \; 0 \; 1 \;\; -1 \; 0'_{p+s}]'. \tag{10}$$

These estimators (9) are specified uniquely as weighted sums of the elements of Y and are, of course, unbiased. The least-squares estimators of $\tau_A - \tau_B$ and $\rho_A - \rho_B$ have sampling variances

$$\text{var}(\widehat{\tau}_A - \widehat{\tau}_B) = w_\tau' w_\tau \sigma^2 \quad \text{and} \quad \text{var}(\widehat{\rho}_A - \widehat{\rho}_B) = w_\rho' w_\rho \sigma^2, \tag{11}$$

respectively.These results can be summarized as follows:

Proposition 2. If the design D is connected then the weighted coefficients of the least-squares estimators of the direct effects contrast and the carry-over effects contrast are given by $w_\tau' = \lambda_\tau'(X'X)^- X'$ and $w_\rho' = \lambda_\rho'(X'X)^- X'$ respectively, where λ_τ', λ_ρ' are given by (10). The least squares contrast estimators are given by (9) and their sampling variances are given by (11)

It should be remarked that Proposition 2 also applies to an eventual cross-over design D_e in the event of missing observations due to subject drop-out, provided that D_e is connected. The proposition is therefore useful for establishing the weights w for eventual designs that occur after subject drop-out from a perpetually connected design. Furthermore it is evident that a choice between competing perpetually connected designs in $\mathcal{D}$ can be made by comparing the corresponding sampling variances for the direct effects $\text{var}(\widehat{\tau}_A - \widehat{\tau}_B)$, specified in (11), which give the usual measure of precision of the estimator in each case.

4. The two-treatment four-period designs with four sequences

4.1. Three planned two-treatment four-period designs with four sequences

To illustrate the results of Section 3 consider the robustness of a design for two treatments which employs $4s_0$ subjects over four periods where, for simplicity but without affecting the general argument, it is assumed that $s_0 = 1$. The problem of design selection for this situation has been considered extensively by many authors, confer Chow and Liu (2008, Section 2.5), Reed (2012) and Jones and Kenward (2015, Section 3.10); however, the robustness of the designs do not appear to have been addressed in detail. Three designs are considered here:

A	B	A	B
A	B	B	A
B	A	B	A
B	A	A	B

Design 4.1.1.

A	B	A	B
B	A	B	A
A	B	B	A
B	A	A	B

Design 4.1.2.

A	B	A	B
B	A	B	A
B	A	B	A
A	B	A	B

Design 4.1.3.

Design 4.1.1 is the optimum design described by Chow and Liu (2008, page 43), Jones and Kenward (2015, Section 3.10) which has optimum cost efficiencies (Yuan and Zhou, 2005) and is recommended for use by the FDA in bioequivalence experiments (FDA, 2001). Design 4.1.2 is one of the designs described by Reed (2012). Design 4.1.3 consists of two replicates of the two-sequence four-period design given in Table 3.22 of Jones and Kenward (2015) which has good estimation properties. Note that Jones and Kenward (2015, Section 3.10) label these three designs 4.4.13, 4.4.23 and 4.4.33 respectively. Design 4.1.1 is perpetually connected but the other two designs are not. In fact designs 4.1.2 and 4.1.3 have the same minimal design, consequently all disconnected eventual designs will have the same lack of estimability of treatment effects which, in these cases, is that neither $\tau_A - \tau_B$ nor $\rho_A - \rho_B$ is estimable. However, the breakdown numbers for these two planned designs are not the same; Design 4.1.2 has breakdown number equal to six and Design 4.1.3 has breakdown number equal to four.

The weight vectors (8) for the treatments direct effects contrast estimator $\widehat{\tau}_A - \widehat{\tau}_B$ specified by (9), with $w = w_\tau$ defined in Proposition 2, for the three designs are specified as follows:

$A\left(\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$	$A\left(\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$
$A\left(\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$	$A\left(\frac{1}{8}\right)$
$B\left(-\frac{1}{8}\right)$	$A\left(\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$	$A\left(\frac{1}{8}\right)$
$B\left(-\frac{1}{8}\right)$	$A\left(\frac{1}{8}\right)$	$A\left(\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$

Design 4.1.1 with (w_τ weights) superimposed.

$A\left(\frac{9}{56}\right)$	$B\left(-\frac{9}{56}\right)$	$A\left(\frac{13}{56}\right)$	$B\left(-\frac{13}{56}\right)$
$B\left(-\frac{5}{56}\right)$	$A\left(\frac{5}{56}\right)$	$B\left(-\frac{1}{56}\right)$	$A\left(\frac{1}{56}\right)$
$A\left(\frac{1}{56}\right)$	$B\left(-\frac{1}{56}\right)$	$B\left(-\frac{17}{56}\right)$	$A\left(\frac{17}{56}\right)$
$B\left(-\frac{5}{56}\right)$	$A\left(\frac{5}{56}\right)$	$A\left(\frac{5}{56}\right)$	$B\left(-\frac{5}{56}\right)$

Design 4.1.2 with (w_τ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{3}{20}\right) & B\left(-\frac{3}{20}\right) & A\left(\frac{3}{20}\right) & B\left(-\frac{3}{20}\right) \\ B\left(-\frac{3}{40}\right) & A\left(\frac{3}{40}\right) & B\left(-\frac{3}{40}\right) & A\left(\frac{3}{40}\right) \\ B\left(-\frac{7}{40}\right) & A\left(\frac{7}{40}\right) & B\left(-\frac{7}{40}\right) & A\left(\frac{7}{40}\right) \\ A\left(\frac{1}{10}\right) & B\left(-\frac{1}{10}\right) & A\left(\frac{1}{10}\right) & B\left(-\frac{1}{10}\right) \end{array}$$

Design 4.1.3 with (w_τ weights) superimposed.

These results show that for Design 4.1.1 the least squares estimator of $\tau_A - \tau_B$ is simply the difference between the mean of the eight measurements on treatment A minus the mean of the eight measurements on treatment B, which is the intuitive estimator. The least squares estimator of $\tau_A - \tau_B$ for Designs 4.1.2 and 4.1.3 are weighted means, which implies that the intuitive estimator is biased in each of these cases.

The sample variances (11) for these designs are $\frac{1}{4}\sigma^2$, $\frac{11}{28}\sigma^2$ and $\frac{11}{40}\sigma^2$ respectively. This shows that Design 4.1.1 is the most efficient design of the three. Design 4.1.3 has smaller variance than Design 4.1.2, thus demonstrating that the preferred design on grounds of minimum variance is not necessarily the preferred design on the grounds of robustness since, at least in this case, it is not the more robust design.

In a similar way the weight vectors (8) for the treatments carry-over effects contrast estimator $\widehat{\rho}_A - \widehat{\rho}_B$ specified by (9), with $w = w_\rho$ defined in Proposition 2, for the three designs are given by:

$$\begin{array}{cccc} A\left(-\frac{1}{22}\right) & B\left(\frac{1}{22}\right) & A\left(\frac{1}{22}\right) & B\left(-\frac{1}{22}\right) \\ A\left(\frac{3}{22}\right) & B\left(-\frac{3}{22}\right) & B\left(\frac{5}{22}\right) & A\left(-\frac{5}{22}\right) \\ B\left(\frac{3}{22}\right) & A\left(-\frac{3}{22}\right) & B\left(-\frac{3}{22}\right) & A\left(\frac{3}{22}\right) \\ B\left(-\frac{5}{22}\right) & A\left(\frac{5}{22}\right) & A\left(-\frac{3}{22}\right) & B\left(\frac{3}{22}\right) \end{array}$$

Design 4.1.1 with (w_ρ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{1}{14}\right) & B\left(-\frac{1}{14}\right) & A\left(\frac{3}{14}\right) & B\left(-\frac{3}{14}\right) \\ B\left(\frac{1}{14}\right) & A\left(-\frac{1}{14}\right) & B\left(\frac{3}{14}\right) & A\left(-\frac{3}{14}\right) \\ A\left(-\frac{3}{14}\right) & B\left(\frac{3}{14}\right) & B\left(-\frac{5}{14}\right) & A\left(\frac{5}{14}\right) \\ B\left(\frac{1}{14}\right) & A\left(-\frac{1}{14}\right) & A\left(-\frac{1}{14}\right) & B\left(\frac{1}{14}\right) \end{array}$$

Design 4.1.2 with (w_ρ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{1}{10}\right) & B\left(-\frac{1}{10}\right) & A\left(\frac{1}{10}\right) & B\left(-\frac{1}{10}\right) \\ B\left(\frac{1}{5}\right) & A\left(-\frac{1}{5}\right) & B\left(\frac{1}{5}\right) & A\left(-\frac{1}{5}\right) \\ B\left(-\frac{1}{5}\right) & A\left(\frac{1}{5}\right) & B\left(-\frac{1}{5}\right) & A\left(\frac{1}{5}\right) \\ A\left(-\frac{1}{10}\right) & B\left(\frac{1}{10}\right) & A\left(-\frac{1}{10}\right) & B\left(\frac{1}{10}\right) \end{array}$$

Design 4.1.3 with (w_ρ weights) superimposed.

The corresponding sample variances (11) for the $\widehat{\rho}_A - \widehat{\rho}_B$ contrast estimators for these designs are $\frac{4}{11}\sigma^2$, $\frac{4}{7}\sigma^2$ and $\frac{2}{5}\sigma^2$ respectively, which are ranked the same as the estimators for the direct effect contrast.

4.2. Two-treatment four-period design with four sequences: Eventual designs

It is interesting and useful to point out that the procedure for determining the coefficients of the contrast estimators and the sample variances outlined in Section 3.3 will apply to the eventual designs when data are missing, provided they are connected, in the same way as the planned design. To illustrate this point the w_τ weights are presented for two eventual designs after drop-out occurs to Design 4.1.1 by the loss of one subject in the third period and by the loss of all four subjects in the third period, i.e. the minimal design.

$$\begin{array}{cccc} A\left(\frac{3}{20}\right) & B\left(-\frac{3}{20}\right) & A\left(\frac{3}{20}\right) & B\left(-\frac{3}{20}\right) \\ A\left(\frac{3}{20}\right) & B\left(-\frac{3}{20}\right) & B\left(-\frac{3}{20}\right) & A\left(\frac{3}{20}\right) \\ B\left(-\frac{1}{10}\right) & A\left(\frac{1}{5}\right) & B\left(-\frac{1}{10}\right) & * \\ B\left(-\frac{1}{5}\right) & A\left(\frac{1}{10}\right) & A\left(\frac{1}{10}\right) & * \end{array}$$

Eventual Design 4.1.1 (w_τ weights superimposed.)

$$\begin{array}{cccc} A\left(\frac{1}{2}\right) & B\left(-\frac{1}{2}\right) & A\left(\frac{1}{2}\right) & B\left(-\frac{1}{2}\right) \\ A\left(\frac{1}{2}\right) & B\left(-\frac{1}{2}\right) & B\left(-\frac{1}{2}\right) & A\left(\frac{1}{2}\right) \\ * & * & * & * \\ * & * & * & * \end{array}$$

Minimal Design 4.1.1 (w_τ weights superimposed.)

Similarly, the w_ρ weights for the two eventual designs after drop-out occurs to Design 4.1.1 by the loss of one subject in the third period and the minimal design are also presented.

$A\left(-\frac{1}{8}\right)$	$B\ (0)$	$A\ (0)$	$B\left(\frac{1}{8}\right)$
$A\left(\frac{1}{8}\right)$	$B\left(-\frac{1}{4}\right)$	$B\left(\frac{1}{4}\right)$	$A\left(-\frac{1}{8}\right)$
$B\left(\frac{1}{4}\right)$	$A\left(-\frac{1}{8}\right)$	$B\left(-\frac{1}{8}\right)$	$*$
$B\left(-\frac{1}{4}\right)$	$A\left(\frac{3}{8}\right)$	$A\left(-\frac{1}{8}\right)$	$*$

Eventual Design 4.1.1 (w_ρ weights superimposed.)

$A\ (-1)$	$B\ (1)$	$A\ (0)$	$B\ (0)$
$A\ (1)$	$B\ (-1)$	$B\ (0)$	$A\ (0)$
$*$	$*$	$*$	$*$
$*$	$*$	$*$	$*$

Minimal Design 4.1.1 (w_ρ weights superimposed.)

It is noticeable that all of the weights for the data that remain in the eventual designs have changed from those in the planned design. Furthermore the sampling variances have increased over the values for the planned design, as one would expect. The displays of the weight vectors for the minimal design are possible only because Design 4.1.1 is perpetually connected.

4.3. The general case

	Design						
Design	4.2.1	4.2.2	4.2.3	4.2.4	4.2.5	4.2.6	4.2.7
4.2.1	4.4.11 4	4.4.12 ∞	4.4.13 ∞	4.4.14 ∞	4.4.15 6	4.4.16 ∞	4.4.17 6
4.2.2		4.4.22 4	4.4.23 6	4.4.24 6	4.4.25 ∞	4.4.26 6	4.4.27 ∞
4.2.3			4.4.33 4	4.4.34 6	4.4.35 ∞	4.4.36 6	4.4.37 ∞
4.2.4				4.4.44 4	4.4.45 ∞	4.4.46 6	4.4.47 ∞
4.2.5					4.4.55 4	4.4.56 ∞	4.4.57 6
4.2.6						4.4.66 4	4.4.67 ∞
4.2.7							4.4.77 4

Table 1: Breakdown numbers for all two-treatment cross-over designs with four periods and four sequences

In general, the four period designs for two treatments with four sequences are considered by Jones and Kenward (2015, Section 3.10) who describe these designs as combinations of pairs of four period designs for two treatments with two sequences, each of which is a dual of the other. Because of the importance of the Jones-Kenward designs and their robustness implications, the Jones-Kenward referencing of these designs is adopted here in this section and in the appendix to this paper.

The Jones-Kenward referencing is as follows. There are seven two-sequence four-period designs, designated 4.2.1 to 4.2.7, and these are listed in the Appendix for ease of reference. The four-sequence four-period design is obtained by combining 4.2.a with 4.2.b and is labelled 4.4.ab, $(a, b = 1, \ldots 7)$. Table 1 presents the breakdown numbers for all of the 28 possible designs. These breakdown numbers are sufficiently high to ensure that none of the eventual designs will be disconnected if only one subject drops out in the third or fourth period; however if two subjects drop out at the third period then seven designs are at risk, viz. Designs 4.4.aa $(a = 1, \ldots, 7)$.

For the two-treatment, four-period designs with four sequences, the set $\mathcal{D}$ of perpetually connected designs contained 12 unique designs, which are listed in the Appendix for reference. Therefore, to choose between these designs, an estimate for the sampling variance of $\tau_A - \tau_B$ can be computed for each perpetually connected design. These estimates are displayed in Table 2, where the designs are ranked by minimum variance. Design 4.4.13 had the lowest

Design	Treatment contrast variance	Breakdown number
4.4.13	$0.250\sigma^2$	∞
4.4.12	$0.275\sigma^2$	∞
4.4.14	$0.288\sigma^2$	∞
4.4.16	$0.288\sigma^2$	∞
4.4.37	$0.315\sigma^2$	∞
4.4.67	$0.333\sigma^2$	∞
4.4.56	$0.341\sigma^2$	∞
4.4.35	$0.344\sigma^2$	∞
4.4.47	$0.418\sigma^2$	∞
4.4.45	$0.458\sigma^2$	∞
4.4.27	$0.571\sigma^2$	∞
4.4.25	$0.603\sigma^2$	∞

Table 2: Sampling treatment contrast variance and breakdown number for all 12 two-treatment four-period four-sequence perpetually connected designs, ranked by order of efficiency

estimate of treatment contrast variance for any of the perpetually connected designs, and can be recommended for an experiment that investigates two treatments over four periods. Interestingly, it appears that specific two-sequence designs that each four-sequence design is made up of perform better than others. Clearly, Design 4.2.1 contributes low variance, as each design which contains these two sequences have lower variance than any other design. It appears that the estimate of treatment contrast variance is a combination of the treatment contrast variance from each two-sequence design. Whilst all designs possess the same properties with respect to robustness to missing values, there is a considerable advantage in choosing Design 4.4.13 or Design 4.4.12 when compared with Design 4.4.27 or Design 4.4.25. Therefore, it is recommended that one of the higher ranked designs is chosen for use in practice.

5. Discussion

Considerable attention has been given to the problems associated with incomplete data in clinical trials due to subject drop-out. It is evident that the concepts of breakdown number and perpetual connectivity are useful aids for assessing the robustness of possible cross-over designs that may be employed in these studies. In this paper it is shown that two-treatment higher-order cross-over designs exist which are robust to missing values, based on these criteria. In particular it is possible to rank the two-treatment designs by robustness, together with minimum variance of the direct effects contrast. This is demonstrated by considering the class of two-treatment, four-period designs with four sequences, arranged as two pairs of dual sequences. The results of Table 2 support the recommendation of the FDA that Design 4.1.1 is the most suitable. It follows that a number, s_0, of replicates of Design 4.1.1 would also be suggested for designs that recruit $4s_0$ participants when $s_0 \geq 2$. Furthermore it is seen that there are other designs which are also perpetually connected and have relatively small sampling variances.

5.1. Criteria of Robustness

The concept of breakdown number of a design to denote the number of observations that need to be lost before the resulting eventual design may be disconnected was introduced by Mahbub Latif *et al.* (2009) in an investigation of robustness properties of microarray designs. An equivalent, if more unwieldy term, is *minimal rank reducing observation set* that was introduced by Godolphin (2004). This concept plays a crucial part in seeking designs which are *maximally robust*, a term due to Ghosh (1982), as described for example by Godolphin and Godolphin (2015). Evidence that the breakdown number is received in the statistical design literature as a useful measure of robustness is provided by Godolphin and Godolphin (2015) and the references therein. The proposal in this paper that perpetual connectivity, which is assigned a breakdown number of ∞, is a limiting ideal property of a breakdown number is a natural extension of this concept which has practical value for design assessment. If no perpetual connected design exists, then there may be circumstances where designs with comparatively low breakdown numbers might be preferred

on grounds of cost or statistical efficiency, however this will be at the risk of a disconnected eventual design. Indeed it appears to be unwise to rely on efficiency considerations alone when planning a design for a cross-over experiment. For example, it should be noted that the variance of Design 4.1.3 is $\frac{11}{40}\sigma^2 = 0.275\sigma^2$ which would rank Design 4.1.3 second on the list of minimum variance perpetually connected designs in Table 2, although the breakdown number for Design 4.1.3 is only $m_D = 4$, i.e. Design 4.1.3 has comparatively poor robustness properties. The authors suggest that Design 4.1.3 is vulnerable to observation loss and should not be recommended in practice, despite its relatively low sampling variance, since any one of the twelve perpetually connected designs do not have the same risk.

Quite apart from the use of the weighted coefficients procedure of Proposition 2 for formulating sampling variances of the treatment contrasts for direct and carry-over effects, there is another property of these weighted values which is helpful when comparing the effects of missing values on connected eventual designs. The output in Section 4.2 shows that these weights change as different observations are lost, and this is useful information for assessing the influence of those observations that remain.

5.2. Locally Efficient Designs

The literature on the optimality and efficiency of cross-over designs includes the recent contributions by Low et al. (1999), Majumdar et al., (2008), Zhao and Majumdar (2012) and Zheng (2013), which study the possibility of subject drop-out and yield some interesting and useful results. The approach of the present paper differs from these works in two ways. Firstly, wherever possible the main objective is to define and then eliminate from consideration all eventual designs that could be disconnected due to drop-out over the third and subsequent periods. The second objective is to identify locally efficient designs, i.e. designs with good properties of design efficiency from the set $\mathcal{D}$ of perpetually connected designs which remain. For example Zheng (2013, page 83) recommends a design for $t = 2$ treatments over $p = 6$ periods for $s = 14$ subjects, designated $d9$ therein, and this is displayed here as Design 5.2.1.

A	B	A	B	A	B	A	B	A	B	A	B	A	B
B	A	B	A	B	A	B	A	B	A	B	A	B	A
B	A	B	A	B	A	B	A	B	A	B	A	B	A
A	B	B	A	B	A	B	A	B	A	B	A	B	A
B	A	A	B	A	B	A	B	A	B	A	B	A	B
A	B	A	B	A	B	A	B	A	B	A	B	A	B

Design 5.2.1. Zheng two-treatment design $d9$

This design has high efficiency and robustness, conditional on the assumption made by Zheng (2013) that there is no subject drop-out in the first four periods and that drop-out is more likely in the final period compared to period 5 in the ratio of 3:2. However, Design 5.2.1 is not perpetually connected so it follows that there will be some disconnected eventual designs. In particular, let the subjects (columns) of the displayed design be labelled consecutively from 1 to 14. If all odd-numbered subjects and subject 2 leave the study at period 3 we get Design 5.2.2:

A	B	A	B	A	B	A	B	A	B	A	B	A	B
B	A	B	A	B	A	B	A	B	A	B	A	B	A
$*$	$*$	$*$	A	$*$	A	$*$	A	$*$	A	$*$	A	$*$	A
$*$	$*$	$*$	A	$*$	A	$*$	A	$*$	A	$*$	A	$*$	A
$*$	$*$	$*$	B	$*$	B	$*$	B	$*$	B	$*$	B	$*$	B
$*$	$*$	$*$	B	$*$	B	$*$	B	$*$	B	$*$	B	$*$	B

Design 5.2.2. Zheng design $d9$ with drop-out

The eventual design, Design 5.2.2, is disconnected. When this occurs, then no unbiased linear estimator of $\tau_A - \tau_B$ or $\rho_A - \rho_B$ is available. Whilst this form of drop-out behaviour may seem extreme, the question of most concern in this case is that the eventual design has 52 remaining measurements, 26 of treatment A and 26 of treatment B, but the structure of this eventual design is such that unbiased linear estimates of these two contrasts cannot be realized.

This situation can be avoided when design selection is restricted to the set $\mathcal{D}$ of perpetually connected designs, which is the procedure recommended by the authors whenever $\mathcal{D}$ is not empty. A perpetually connected design is

given by Design 5.2.3 which consists of three copies of dual block *AABBBA* and *BBAAAB* and four copies of dual block *ABBAAB* and *BAABBBA*.

A	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*
A	*B*	*B*	*A*	*A*	*B*	*B*	*A*	*A*	*B*	*B*	*A*	*B*	*A*
B	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*	*B*	*A*
B	*A*	*A*	*B*	*B*	*A*	*A*	*B*	*B*	*A*	*A*	*B*	*A*	*B*
B	*A*	*A*	*B*	*B*	*A*	*A*	*B*	*B*	*A*	*A*	*B*	*A*	*B*
A	*B*	*B*	*A*	*A*	*B*	*B*	*A*	*A*	*B*	*B*	*A*	*B*	*A*

Design 5.2.3. Alternative to Zheng design *d*9

Although Design 5.2.3 is chosen from a smaller universal set than Design 5.2.1, it turns out that the two designs have similar properties of estimator efficiency. The pair of sampling variances $\{\mathrm{Var}(\widehat{\tau}_A - \widehat{\tau}_B),\ \mathrm{Var}(\widehat{\rho}_A - \widehat{\rho}_B)\}$ are given by $\{0.04792\sigma^2,\ 0.05949\sigma^2\}$ for Design 5.2.1 and $\{0.04766\sigma^2,\ 0.05915\sigma^2\}$ for Design 5.2.3. Furthermore, Design 5.2.3 is a candidate for selection since it belongs to the set $\mathcal{D}$, therefore it has the property that there are no disconnected eventual designs, whatever the drop-out mechanism, provided that all subjects stay in the experiment for the first two periods. This is an important and worthwhile property which is not shared by Design 5.2.1 nor any other design that does not belong to $\mathcal{D}$ and is not perpetually connected.

5.3. The Estimation Procedure

The representation (1) of the cross-over design is the traditional fixed-effects model recommended by regulatory guidelines. The estimation of parametric combinations of interest, in particular the estimates of the contrasts $\tau_A - \tau_B$ and $\rho_A - \rho_B$, is achieved by standard least-squares as described, for example, in Section 3.3. If drop-out occurs but the eventual design is connected, and all subjects stay with the study for at least two periods then the least-squares estimates (9) are complete in the sense that they involve all available observations. It follows that all measurements taken from subjects who drop out of the study, as well as all measurements taken from subjects who complete their treatment sequences, are utilized in the contrast estimates. This is consistent with the recommendation of Patel (1985) and others, that the practice of removing the results of subjects who drop out and do not complete their whole sequence should be discontinued.

In common with other works, for example Majumdar et al.(2008), the approach given in this paper does not require an estimate of the unrealized value of any observation which is lost due to subject drop-out in order to obtain the least-squares estimates of contrasts, in this case $\tau_A - \tau_B$ and $\rho_A - \rho_B$. Note that the estimation of missing values as linear functions of the realized observations is equivalent to forming additional elements of the space $\mathcal{R}$ from those vectors which remain after subjects have dropped out. This applies whether the eventual design is connected or otherwise. Of course, if the eventual design is disconnected then $\dim\mathcal{R}$ is strictly less than $\dim\mathcal{R}_{\mathrm{plan}}$, and it will not be possible in this case to increase $\dim\mathcal{R}$ by adding any number of linear combinations of the existing elements of $\mathcal{R}$.

5.4. Assumptions Required of the Approach

The limitations of this approach stem from the need to make two assumptions, described in detail in Section 2.2. It is not always plausible that there will be no subject drop-out in the first two periods of the study, especially for experiments where there is extensive follow-up time between treatment being administered and response measured. Furthermore, the assumption that all missing data is unrelated to a positive or negative treatment reaction will not necessarily hold for all circumstances. If a participant reacts badly, or well, to a single treatment application and fails to return for the second period then perhaps this is useful information for the experiment, although it would not be classified as MAR. However, a formal assumption that subject drop-out is MNAR may need a further assumption that carry-over is a non-existent effect. Given that higher-order designs are widely used in situations where carry-over is expected, this assumption may seem undesirable. Additionally, the permitting of drop-out in the first or second periods may require a restriction on the loss of data in later periods, which is perhaps less preferable. The assumptions of the paper seem reasonable for many practical situations and, whilst they may be unrealized in some experimental conditions, it is believed that these ideas and concepts provide a useful starting point in this area of research.

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Appendix

Two-treatment, Four-period, Two-sequence Designs

All seven dual two-treatment, four-period, two-sequence designs are given below with the Jones-Kenward labels 4.2.a, $(a, b = 1, \ldots 7)$. These designs are used to generate all 28 dual two-treatment, four-period, four sequence designs discussed in Section 4.

$A\ B$	$A\ B$	$A\ B$	$A\ B$	$A\ B$	$A\ B$	$A\ B$
$A\ B$	$B\ A$	$B\ A$	$B\ A$	$A\ B$	$B\ A$	$A\ B$
$B\ A$	$A\ B$	$B\ A$	$A\ B$	$B\ A$	$B\ A$	$A\ B$
$B\ A$	$B\ A$	$A\ B$	$A\ B$	$A\ B$	$B\ A$	$B\ A$
Design 4.2.1.	**Design 4.2.2.**	**Design 4.2.3.**	**Design 4.2.4.**	**Design 4.2.5.**	**Design 4.2.6.**	**Design 4.2.7.**

Two-treatment, Four-period, Four-sequence Designs

The set $\mathcal{D}$ of twelve perpetually connected designs discussed in Table's 1 and 2 and produced through the combination of 4.2.a with 4.2.b, and they are labelled 4.4.ab, $(a, b = 1, \ldots 7)$. All twelve designs are displayed below.

$A\ B\ A\ B$	$A\ B\ A\ B$	$A\ B\ A\ B$	$A\ B\ A\ B$
$A\ B\ B\ A$	$A\ B\ B\ A$	$A\ B\ B\ A$	$A\ B\ B\ A$
$B\ A\ A\ B$	$B\ A\ B\ A$	$B\ A\ A\ B$	$B\ A\ B\ A$
$B\ A\ B\ A$	$B\ A\ A\ B$	$B\ A\ A\ B$	$B\ A\ B\ A$
Design 4.4.12.	**Design 4.4.13.**	**Design 4.4.14.**	**Design 4.4.16.**

$A\ B\ A\ B$	$A\ B\ A\ B$	$A\ B\ A\ B$	$A\ B\ A\ B$
$B\ A\ A\ B$	$B\ A\ A\ B$	$B\ A\ A\ B$	$B\ A\ A\ B$
$B\ A\ B\ A$	$A\ B\ B\ A$	$B\ A\ B\ A$	$B\ A\ A\ B$
$A\ B\ B\ A$	$B\ A\ A\ B$	$A\ B\ A\ B$	$A\ B\ B\ A$
Design 4.4.25.	**Design 4.4.27.**	**Design 4.4.35.**	**Design 4.4.37.**

$A\ B\ A\ B$	$A\ B\ A\ B$	$A\ B\ A\ B$	$A\ B\ A\ B$
$B\ A\ A\ B$	$B\ A\ A\ B$	$A\ B\ B\ A$	$B\ A\ A\ B$
$A\ B\ B\ A$	$A\ B\ A\ B$	$B\ A\ B\ A$	$B\ A\ A\ B$
$A\ B\ A\ B$	$A\ B\ B\ A$	$A\ B\ B\ A$	$B\ A\ B\ A$
Design 4.4.45.	**Design 4.4.47.**	**Design 4.4.56.**	**Design 4.4.67.**

Least Square Weights for Direct Treatment Contrast $\tau_A - \tau_B$

$$\begin{array}{cccc} A\left(\frac{1}{8}\right) & B\left(-\frac{1}{8}\right) & A\left(\frac{1}{8}\right) & B\left(-\frac{1}{8}\right) \\ A\left(\frac{7}{40}\right) & B\left(-\frac{7}{40}\right) & B\left(-\frac{1}{10}\right) & A\left(\frac{1}{10}\right) \\ B\left(-\frac{1}{10}\right) & A\left(\frac{1}{10}\right) & A\left(\frac{3}{40}\right) & B\left(-\frac{3}{40}\right) \\ B\left(-\frac{1}{5}\right) & A\left(\frac{1}{5}\right) & B\left(-\frac{1}{10}\right) & A\left(\frac{1}{10}\right) \end{array}$$

Design 4.4.12 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{1}{8}\right) & B\left(-\frac{1}{8}\right) & A\left(\frac{1}{8}\right) & B\left(-\frac{1}{8}\right) \\ B\left(\frac{1}{8}\right) & A\left(-\frac{1}{8}\right) & A\left(-\frac{1}{8}\right) & B\left(\frac{1}{8}\right) \\ B\left(-\frac{1}{8}\right) & A\left(\frac{1}{8}\right) & B\left(-\frac{1}{8}\right) & A\left(\frac{1}{8}\right) \\ A\left(-\frac{1}{8}\right) & B\left(\frac{1}{8}\right) & B\left(\frac{1}{8}\right) & A\left(-\frac{1}{8}\right) \end{array}$$

Design 4.4.13 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{43}{306}\right) & B\left(-\frac{43}{306}\right) & A\left(\frac{7}{102}\right) & B\left(-\frac{7}{102}\right) \\ B\left(\frac{47}{306}\right) & A\left(-\frac{47}{306}\right) & A\left(\frac{}{7}34\right) & B\left(\frac{7}{34}\right) \\ B\left(-\frac{41}{306}\right) & A\left(\frac{41}{306}\right) & B\left(\frac{1}{18}\right) & A\left(-\frac{1}{18}\right) \\ A\left(-\frac{49}{306}\right) & B\left(\frac{49}{306}\right) & B\left(\frac{25}{306}\right) & A\left(-\frac{25}{306}\right) \end{array}$$

Design 4.4.14 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{47}{290}\right) & B\left(-\frac{47}{290}\right) & A\left(\frac{63}{290}\right) & B\left(-\frac{63}{290}\right) \\ B\left(\frac{7}{58}\right) & A\left(-\frac{7}{58}\right) & A\left(-\frac{37}{290}\right) & B\left(\frac{37}{290}\right) \\ B\left(-\frac{53}{290}\right) & A\left(\frac{53}{290}\right) & B\left(-\frac{13}{290}\right) & A\left(\frac{13}{290}\right) \\ A\left(-\frac{1}{10}\right) & B\left(\frac{1}{10}\right) & B\left(-\frac{13}{290}\right) & A\left(\frac{13}{290}\right) \end{array}$$

Design 4.4.16 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{35}{146}\right) & B\left(-\frac{35}{146}\right) & A\left(\frac{13}{146}\right) & B\left(-\frac{13}{146}\right) \\ B\left(-\frac{17}{146}\right) & A\left(\frac{17}{146}\right) & A\left(\frac{49}{146}\right) & B\left(-\frac{49}{146}\right) \\ B\left(-\frac{1}{146}\right) & A\left(\frac{1}{146}\right) & B\left(-\frac{39}{146}\right) & A\left(\frac{39}{146}\right) \\ A\left(-\frac{17}{146}\right) & B\left(\frac{17}{146}\right) & B\left(-\frac{23}{146}\right) & A\left(\frac{23}{146}\right) \end{array}$$

Design 4.4.25 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{3}{14}\right) & B\left(-\frac{3}{14}\right) & A\left(-\frac{1}{14}\right) & B\left(\frac{1}{14}\right) \\ B\left(-\frac{1}{14}\right) & A\left(\frac{1}{14}\right) & A\left(\frac{3}{14}\right) & B\left(-\frac{3}{14}\right) \\ A\left(-\frac{1}{14}\right) & B\left(\frac{1}{14}\right) & B\left(\frac{3}{14}\right) & A\left(-\frac{3}{14}\right) \\ B\left(-\frac{1}{14}\right) & A\left(\frac{1}{14}\right) & A\left(-\frac{5}{14}\right) & B\left(\frac{5}{14}\right) \end{array}$$

Design 4.4.27 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{49}{258}\right) & B\left(-\frac{49}{258}\right) & A\left(\frac{17}{258}\right) & B\left(-\frac{17}{258}\right) \\ B\left(-\frac{19}{258}\right) & A\left(\frac{19}{258}\right) & A\left(\frac{37}{258}\right) & B\left(-\frac{37}{258}\right) \\ B\left(-\frac{59}{258}\right) & A\left(\frac{59}{258}\right) & B\left(-\frac{17}{86}\right) & A\left(\frac{17}{86}\right) \\ A\left(\frac{29}{258}\right) & B\left(-\frac{29}{258}\right) & A\left(-\frac{1}{86}\right) & B\left(\frac{1}{86}\right) \end{array}$$

Design 4.4.35 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{31}{178}\right) & B\left(-\frac{31}{178}\right) & A\left(\frac{5}{178}\right) & B\left(-\frac{5}{178}\right) \\ B\left(-\frac{13}{178}\right) & A\left(\frac{13}{178}\right) & A\left(\frac{17}{178}\right) & B\left(-\frac{17}{178}\right) \\ B\left(-\frac{37}{178}\right) & A\left(\frac{37}{178}\right) & A\left(\frac{17}{178}\right) & B\left(-\frac{17}{178}\right) \\ A\left(\frac{19}{178}\right) & B\left(-\frac{19}{178}\right) & B\left(-\frac{39}{178}\right) & A\left(\frac{39}{178}\right) \end{array}$$

Design 4.4.37 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{1}{12}\right) & B\left(-\frac{1}{12}\right) & A\left(\frac{1}{12}\right) & B\left(-\frac{1}{12}\right) \\ B\left(-\frac{1}{4}\right) & A\left(\frac{1}{4}\right) & A\left(\frac{5}{24}\right) & B\left(-\frac{5}{24}\right) \\ A\left(-\frac{1}{24}\right) & B\left(\frac{1}{24}\right) & B\left(-\frac{1}{4}\right) & A\left(\frac{1}{4}\right) \\ A\left(\frac{5}{24}\right) & B\left(-\frac{5}{24}\right) & A\left(-\frac{1}{24}\right) & B\left(\frac{1}{24}\right) \end{array}$$

Design 4.4.45 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{5}{68}\right) & B\left(-\frac{5}{68}\right) & A\left(\frac{1}{68}\right) & B\left(-\frac{1}{68}\right) \\ B\left(-\frac{15}{68}\right) & A\left(\frac{15}{68}\right) & A\left(\frac{9}{68}\right) & B\left(-\frac{9}{68}\right) \\ A\left(-\frac{3}{68}\right) & B\left(\frac{3}{68}\right) & A\left(\frac{9}{68}\right) & B\left(-\frac{9}{68}\right) \\ A\left(\frac{13}{68}\right) & B\left(-\frac{13}{68}\right) & B\left(-\frac{19}{68}\right) & A\left(\frac{19}{68}\right) \end{array}$$

Design 4.4.47 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{5}{68}\right) & B\left(-\frac{5}{68}\right) & A\left(\frac{1}{68}\right) & B\left(-\frac{1}{68}\right) \\ A\left(-\frac{15}{68}\right) & B\left(\frac{15}{68}\right) & B\left(\frac{9}{68}\right) & A\left(-\frac{9}{68}\right) \\ B\left(-\frac{3}{68}\right) & A\left(\frac{3}{68}\right) & B\left(\frac{9}{68}\right) & A\left(-\frac{9}{68}\right) \\ A\left(\frac{13}{68}\right) & B\left(-\frac{13}{68}\right) & B\left(-\frac{19}{68}\right) & A\left(\frac{19}{68}\right) \end{array}$$

Design 4.4.56 with ($\mathbf{w}_\tau$ weights) superimposed.

$$\begin{array}{cccc} A\left(\frac{1}{4}\right) & B\left(-\frac{1}{4}\right) & A\left(\frac{1}{12}\right) & B\left(-\frac{1}{12}\right) \\ B\left(-\frac{1}{12}\right) & A\left(\frac{1}{12}\right) & A\left(\frac{1}{12}\right) & B\left(-\frac{1}{12}\right) \\ B\left(-\frac{1}{12}\right) & A\left(\frac{1}{12}\right) & A\left(\frac{1}{12}\right) & B\left(-\frac{1}{12}\right) \\ B\left(-\frac{1}{12}\right) & A\left(\frac{1}{12}\right) & B\left(-\frac{1}{4}\right) & A\left(\frac{1}{4}\right) \end{array}$$

Design 4.4.67 with ($\mathbf{w}_\tau$ weights) superimposed.

Least Square Weights for Carry-over Treatment Contrast $\rho_A - \rho_B$

$A\ (0)$	$B\ (0)$	$A\ (0)$	$B\ (0)$
$A\ \left(\frac{1}{5}\right)$	$B\ \left(-\frac{1}{5}\right)$	$B\ \left(\frac{1}{10}\right)$	$A\ \left(-\frac{1}{10}\right)$
$B\ \left(\frac{1}{10}\right)$	$A\ \left(-\frac{1}{10}\right)$	$A\ \left(-\frac{1}{5}\right)$	$B\ \left(\frac{1}{5}\right)$
$B\ \left(-\frac{3}{10}\right)$	$A\ \left(\frac{3}{10}\right)$	$B\ \left(\frac{1}{10}\right)$	$A\ \left(-\frac{1}{10}\right)$

Design 4.4.12 with (w_ρ weights) superimposed.

$A\ \left(-\frac{1}{22}\right)$	$B\ \left(\frac{1}{22}\right)$	$A\ \left(\frac{1}{22}\right)$	$B\ \left(-\frac{1}{22}\right)$
$B\ \left(\frac{3}{22}\right)$	$A\ \left(-\frac{3}{22}\right)$	$A\ \left(\frac{5}{22}\right)$	$B\ \left(-\frac{5}{22}\right)$
$B\ \left(\frac{3}{22}\right)$	$A\ \left(-\frac{3}{22}\right)$	$B\ \left(-\frac{3}{22}\right)$	$A\ \left(\frac{3}{22}\right)$
$A\ \left(-\frac{5}{22}\right)$	$B\ \left(\frac{5}{22}\right)$	$B\ \left(-\frac{3}{22}\right)$	$A\ \left(\frac{3}{22}\right)$

Design 4.4.13 with (w_ρ weights) superimposed.

$A\ \left(-\frac{5}{153}\right)$	$B\ \left(\frac{5}{153}\right)$	$A\ \left(-\frac{2}{51}\right)$	$B\ \left(\frac{2}{51}\right)$
$B\ \left(\frac{23}{153}\right)$	$A\ \left(-\frac{23}{153}\right)$	$A\ \left(\frac{2}{17}\right)$	$B\ \left(-\frac{2}{17}\right)$
$B\ \left(\frac{19}{153}\right)$	$A\ \left(-\frac{19}{153}\right)$	$B\ \left(-\frac{2}{9}\right)$	$A\ \left(\frac{2}{9}\right)$
$A\ \left(-\frac{37}{153}\right)$	$B\ \left(\frac{37}{153}\right)$	$B\ \left(\frac{22}{153}\right)$	$A\ \left(-\frac{22}{153}\right)$

Design 4.4.14 with (w_ρ weights) superimposed.

$A\ \left(-\frac{13}{145}\right)$	$B\ \left(\frac{13}{145}\right)$	$A\ \left(-\frac{2}{145}\right)$	$B\ \left(\frac{2}{145}\right)$
$B\ \left(\frac{3}{29}\right)$	$A\ \left(-\frac{3}{29}\right)$	$A\ \left(\frac{38}{145}\right)$	$B\ \left(-\frac{38}{145}\right)$
$B\ \left(\frac{27}{145}\right)$	$A\ \left(-\frac{27}{145}\right)$	$B\ \left(-\frac{18}{145}\right)$	$A\ \left(\frac{18}{145}\right)$
$A\ \left(-\frac{1}{5}\right)$	$B\ \left(\frac{1}{5}\right)$	$B\ \left(-\frac{18}{145}\right)$	$A\ \left(\frac{18}{145}\right)$

Design 4.4.16 with (w_ρ weights) superimposed.

$A\ \left(\frac{11}{73}\right)$	$B\ \left(-\frac{11}{73}\right)$	$A\ \left(\frac{2}{73}\right)$	$B\ \left(-\frac{2}{73}\right)$
$B\ \left(\frac{3}{73}\right)$	$A\ \left(-\frac{3}{73}\right)$	$A\ \left(\frac{30}{73}\right)$	$B\ \left(-\frac{30}{73}\right)$
$B\ \left(-\frac{17}{73}\right)$	$A\ \left(\frac{17}{73}\right)$	$B\ \left(-\frac{6}{73}\right)$	$A\ \left(\frac{6}{73}\right)$
$A\ \left(\frac{3}{73}\right)$	$B\ \left(-\frac{3}{73}\right)$	$B\ \left(-\frac{26}{73}\right)$	$A\ \left(\frac{26}{73}\right)$

Design 4.4.25 with (w_ρ weights) superimposed.

$A\ \left(\frac{1}{7}\right)$	$B\ \left(-\frac{1}{7}\right)$	$A\ \left(-\frac{2}{7}\right)$	$B\ \left(\frac{2}{7}\right)$
$B\ \left(\frac{1}{7}\right)$	$A\ \left(-\frac{1}{7}\right)$	$A\ \left(\frac{2}{7}\right)$	$B\ \left(-\frac{2}{7}\right)$
$A\ \left(-\frac{3}{7}\right)$	$B\ \left(\frac{3}{7}\right)$	$B\ \left(\frac{2}{7}\right)$	$A\ \left(-\frac{2}{7}\right)$
$B\ \left(\frac{1}{7}\right)$	$A\ \left(-\frac{1}{7}\right)$	$A\ \left(-\frac{2}{7}\right)$	$B\ \left(\frac{2}{7}\right)$

Design 4.4.27 with (w_ρ weights) superimposed.

$A\ \left(\frac{17}{129}\right)$	$B\ \left(-\frac{17}{129}\right)$	$A\ \left(-\frac{2}{129}\right)$	$B\ \left(\frac{2}{129}\right)$
$B\ \left(\frac{25}{129}\right)$	$A\ \left(-\frac{25}{129}\right)$	$A\ \left(\frac{26}{129}\right)$	$B\ \left(-\frac{26}{129}\right)$
$B\ \left(-\frac{31}{129}\right)$	$A\ \left(\frac{31}{129}\right)$	$B\ \left(\frac{2}{43}\right)$	$A\ \left(-\frac{2}{43}\right)$
$A\ \left(-\frac{11}{129}\right)$	$B\ \left(\frac{11}{129}\right)$	$A\ \left(-\frac{10}{43}\right)$	$B\ \left(\frac{10}{43}\right)$

Design 4.4.35 with (w_ρ weights) superimposed.

$A\ \left(\frac{13}{89}\right)$	$B\ \left(-\frac{13}{89}\right)$	$A\ \left(-\frac{18}{89}\right)$	$B\ \left(\frac{18}{89}\right)$
$B\ \left(\frac{29}{89}\right)$	$A\ \left(-\frac{29}{89}\right)$	$A\ \left(\frac{10}{89}\right)$	$B\ \left(-\frac{10}{89}\right)$
$B\ \left(-\frac{27}{89}\right)$	$A\ \left(\frac{27}{89}\right)$	$A\ \left(\frac{10}{89}\right)$	$B\ \left(-\frac{10}{89}\right)$
$A\ \left(-\frac{15}{89}\right)$	$B\ \left(\frac{15}{89}\right)$	$B\ \left(-\frac{2}{89}\right)$	$A\ \left(\frac{2}{89}\right)$

Design 4.4.37 with (w_ρ weights) superimposed.

$A\ (0)$	$B\ (0)$	$A\ (0)$	$B\ (0)$
$B\ (0)$	$A\ (0)$	$A\ \left(\frac{1}{4}\right)$	$B\ \left(-\frac{1}{4}\right)$
$A\ \left(-\frac{1}{4}\right)$	$B\ \left(\frac{1}{4}\right)$	$B\ (0)$	$A\ (0)$
$A\ \left(\frac{1}{4}\right)$	$B\ \left(-\frac{1}{4}\right)$	$A\ \left(-\frac{1}{4}\right)$	$B\ \left(\frac{1}{4}\right)$

Design 4.4.45 with (w_ρ weights) superimposed.

$A\ \left(-\frac{1}{34}\right)$	$B\ \left(\frac{1}{34}\right)$	$A\ \left(-\frac{7}{34}\right)$	$B\ \left(\frac{7}{34}\right)$
$B\ \left(-\frac{3}{34}\right)$	$A\ \left(\frac{5}{34}\right)$	$A\ \left(-\frac{5}{34}\right)$	$B\ \left(-\frac{5}{34}\right)$
$A\ \left(-\frac{13}{34}\right)$	$B\ \left(\frac{13}{34}\right)$	$A\ \left(\frac{5}{34}\right)$	$B\ \left(-\frac{5}{34}\right)$
$A\ \left(\frac{11}{34}\right)$	$B\ \left(-\frac{11}{34}\right)$	$B\ \left(-\frac{3}{34}\right)$	$A\ \left(\frac{3}{34}\right)$

Design 4.4.47 with (w_ρ weights) superimposed.

$A\ \left(-\frac{1}{34}\right)$	$B\ \left(\frac{1}{34}\right)$	$A\ \left(-\frac{7}{34}\right)$	$B\ \left(\frac{7}{34}\right)$
$A\ \left(\frac{3}{34}\right)$	$B\ \left(-\frac{3}{34}\right)$	$B\ \left(\frac{5}{34}\right)$	$A\ \left(-\frac{5}{34}\right)$
$B\ \left(-\frac{13}{34}\right)$	$A\ \left(\frac{13}{34}\right)$	$B\ \left(\frac{5}{34}\right)$	$A\ \left(-\frac{5}{34}\right)$
$A\ \left(\frac{11}{34}\right)$	$B\ \left(-\frac{11}{34}\right)$	$B\ \left(-\frac{3}{34}\right)$	$A\ \left(\frac{3}{34}\right)$

Design 4.4.56 with (w_ρ weights) superimposed.

$A\ \left(\frac{1}{14}\right)$	$B\ \left(-\frac{1}{14}\right)$	$A\ \left(-\frac{3}{14}\right)$	$B\ \left(\frac{3}{14}\right)$
$B\ \left(\frac{5}{14}\right)$	$A\ \left(-\frac{5}{14}\right)$	$A\ \left(\frac{1}{14}\right)$	$B\ \left(-\frac{1}{14}\right)$
$B\ \left(-\frac{3}{14}\right)$	$A\ \left(\frac{3}{14}\right)$	$A\ \left(\frac{1}{14}\right)$	$B\ \left(-\frac{1}{14}\right)$
$B\ \left(-\frac{3}{14}\right)$	$A\ \left(\frac{3}{14}\right)$	$B\ \left(\frac{1}{14}\right)$	$A\ \left(-\frac{1}{14}\right)$

Design 4.4.67 with (w_ρ weights) superimposed.

References

Bate, S.T., Godolphin, E.J., Godolphin J.D., 2008. Choosing cross-over designs when few subjects are available. Comput Stat Data Analysis. 52, 1572-1586.

Chow, S.C., Liu J.P., 2008. Design and analysis of bioavailability and bioequivalence studies. CRC Press.
European Medicines Agency, 2010. Guideline on the investigation of bioequivalence. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500070039.pdf
Food and Drug Administration, 2001. Guideline for industry: statistical approaches to establishing bioequivalence. Available from: https://www.fda.gov/downloads/drugs/guidances/ucm070244.pdf
Fleiss J.L., 1989. A critique of recent research on the two-treatment crossover design. Controlled Clinical Trials. 10, 237-243.
Freeman P.R., 1989. The performance of the two-stage analysis of the two-treatment, two-period crossover trials. Statistics in Medicine, 8, 1421-1432.
Godolphin J.D., 2004. Simple pilot procedures for the avoidance of disconnected experimental designs. Applied Statistics. 53, 133-147.
Godolphin J.D., 2013. On the connectivity problem for *m*-way designs. J. Statistical Theory and Practice. 7, 732-744.
Godolphin J.D., Godolphin E.J., 2015. The use of treatment concurrences to assess robustness of binary block designs against the loss of whole blocks. Aust N. Z. J. Statistics. 57, 225-239.
Godolphin P.J., Godolphin E.J., 2017. Robustness of crossover trials against subject drop-out Examples of perpetually connected designs. Statistical Methods in Medical Research. (available on-line at: http://journals.sagepub.com/doi/full/10.1177/0962280217736541)
Ghosh, S. 1982. Robustness of designs against the unavailability of data. J. Statist. Plann. Inference 6, 29-32.
Hedayat A.S., Stufken J., 2003. Optimal and efficient cross-over designs under different assumptions about the carryover effects. Journal of Biopharmaceutical Statistics. 13, 519-528.
Hills M., Armitage P., 1979. The two-period cross-over clinical trial. Br J Clin Pharmacol. 8, 7-20.
Ho W.K., Matthews J.N.S., Henderson R., Farewell D., Rodgers L.R., 2012. Dropouts in the AB/BA cross-over design. Statistics in Medicine. 31, 1675-1687.
Jones B., Kenward G.M., 2015. Design and Analysis of Cross-Over Trials. 3rd edn. Monographs on Statistics and Applied Probability 138. CRC Press.
Kunert J., 1991. Cross-over designs for two treatments and correlated errors. Biometrika. 78, 315-324.
Kushner H.B., 1997. Optimality and efficiency of two-treatment repeated measurements designs. Biometrika. 84, 455-468.
Little R.J.A., Rubin D.B., 2002. Statistical analysis with missing data. 2nd edn. Wiley Series in Probability and Statistics. John Wiley and Sons.
Low J.L., Lewis S.M., Prescott, P. 1999. Assessing robustness of crossover designs to subjects dropping out. Stat Comput. 9, 219-227.
Mahbub Latif A.H.M., Bretz F., Brunner E., 2009. Robustness considerations in selecting two-color microarray designs. Bioinformatics. 25, 2355-2361.
Majumdar D., Dean A.M., Lewis S.M., 2008. Uniformly balanced repeated measurements designs in the presence of subject dropout. Stat. Sinica. 18, 235-253.
Matthews J.N.S., 1987. Optimal crossover designs for the comparison of two treatments in the presence of carryover effects and auto-correlated errors. Biometrika. 74, 311-320. Correction (1988), 75, 396.
Matthews J.N.S., Henderson R., 2013. Two-period, two-treatment crossover designs subject to non-ignorable missing data. Biostatistics. 14, 626-638.
Molenberghs G., Kenward G.M., 2007. Missing Data in Clinical Studies. Statistics in Practice. John Wiley and Sons.
National Academy of Sciences, 2010. The Prevention and Treatment of Missing Data in Clinical Trials. Washington, D.C. National Academies Press.
Patel H.I., 1985. Analysis of incomplete data in a two-period cross-over design with reference to clinical trials. Biometrika. 72, 411-418.
Reed J.F., 2012. Four-period cross-over designs. Journal of Modern Applied Statistical methods. 11, 274-278.
Rosenkranz G.K., 2014. Analysis of cross-over studies with missing data. Statistical Methods in Medical Research. 24, 420-433.
Searle S.R., 1971. Linear Models. New York: Wiley.
Senn S., 2001. Cross-over trials in drug development: theory and practice. Journal of Statistical Planning and Inference. 96, 29-40.
Shih W.J., Aisner J., 2015. Statistical design and analysis of clinical trials: principles and methods. CRC press.
Shih W.J., Quan H., 1997. Testing for treatment differences with drop-outs present in clinical trials: a composite approach. Statistics in Medicine. 16, 1225-1239.
Srivastava J.N., Anderson D.A. (1970), Some basic properties of multidimensional partially balanced designs. Ann. Math. Statistics. 41, 1438-1445.
Yuan Y., Zhou J., 2005. Cost efficient higher order cross-over designs for two-treatment clinical trials. Pharmaceutical Statistics. 4, 245-252.
Zheng W. (2013), Universally optimal crossover designs under subject dropout. Ann. Statistics. 41, 63-90.
Zhou J., Yuan Y., Reynolds R., et al., 2006. Cost-efficient higher order crossover designs in comparative bioavailability studies. Clinical pharmacokinetics. 45, 623-632.
Zhou S., Majumdar D., 2012. On uniformly balanced crossover designs efficient under subject dropout. J. Statistical Theory and Practice. 6 178-189.