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A Case Study on the Optimal Design of Clinical Pharmacology Trials with Restrictions on the Dosing Schedule

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A clinical pharmacology trial, which examines the safety and pharmacodynamics of an investigational drug, is typically the first time that the drug is administered to humans. We are, therefore, often forced to maintain some restrictions on the trial conditions; for example, incremental doses in succeeding stages may be necessary when safety is concerned, and the repetition of the treatment on the same subject may be restricted in terms of the imposition on and convenience of subjects. The present paper investigated optimal trial designs under such restrictions, adopting D_s -optimality (D -optimality for subset) as the criterion.

In order to identify the optimal design, all admissible designs that satisfy the restrictions were listed in a lexical order and their optimality was compared. As a result, it was revealed that a relatively high number of subjects were allocated lower doses in the optimal design when the increment restriction was regarded as relevant, whereas more reasonable designs were identified as optimal when the restrictions were modified.

Key words: clinical pharmacology trial; dosing schedule; D_s -optimal design; enumeration algorithm.

1. Introduction

The primary objective of clinical pharmacology studies at the early drug development stage is investigating the safety and pharmacological effects of potential pharmaceutical products (investigational drugs) on humans.

In these studies, drugs are administered to humans for the first time. Owing to the potential risks and burdens involved, such trials are conducted under various restrictions, for example, ethical limitations on the number of subjects, administration of only a few doses to each subject, and gradual increases in dosage.

In a case encountered by the first author of the present paper (referred to as the “motivating case”), owing to some restrictions, the standard designs described in popular literature (Jones, 1989; Peace, 1998), such as a crossover design with the same number of subjects in each group or a balanced incomplete block design wherein the dosage escalation is disregarded, could not be applied.

Buoen et al. (2005) reported that it is not easy to identify the most suitable design and method of evaluation for a clinical trial and to ascertain the methods for collecting the maximum information. They also reported that the majority of the designs are conservative and seem to be based on habit and preference instead of the statistical and scientific rationale needed to optimize the first human clinical trials.

For the purpose of obtaining optimal designs, however, optimal design theory is applied in clinical trials. In the field of cancer research, Bayesian optimal designs are provided for the efficient estimation of the maximum tolerable dose for cancer phase I clinical trials by using optimal design theory (Haines et al., 2003). Whitehead and Zhou (2001) develop a Bayesian method for finding out the optimal doses for a dose-escalation study in healthy volunteers. This method also uses the optimal design theory for identifying the optimal choice of doses.

In longitudinal studies, an optimal design approach will be used to find the optimal number of repeated measurements (sampling time points) and allocations to maximize the information for the estimation of the parameters in the statistical model (Tekle et al., 2008; Winkens et al., 2005). Ortega-Azurdoy et al. (2008) estimate the efficiency loss if a D -optimal design for complete data is used when the data contain dropouts.

However, none of these designs were considered to be appropriate for the motivating case and, as a result, a dosing schedule was adopted without considering optimality. Upon the completion of the clinical trial, we investigated how the optimal dosing schedule (henceforth referred to as the optimal design) can be determined. Our strategy was to compare all the admissible designs with a criterion for precision in the estimation of fixed effects in the model. Since there are a considerable number of admissible cases, we devised an efficient enumeration algorithm while taking into account the given restrictions. A characteristic feature of the realized algorithm is that it limits the choice of the dosing schedule, as will be explained later. We considered the adopted strategy and our contrivance to be worth publishing as a direct reference for trial statisticians, which is the motivation behind this paper.

In what follows, the motivating case is introduced in Section 2, and the restrictions prevalent in this case are formulated in Section 3. An enumeration algorithm and the optimal designs under various optimality criteria are explained in Section 4; the nature of the optimal design is then examined in Section 5, which is followed by a discussion in Section 6.

2. Motivating case for this study

The case in question was a phase I clinical trial carried out in Japan, and its purpose was to test an investigational drug for stress urinary incontinence (SUI). The dosages of investigational drug to be tested are four dosages (d_1, d_2, d_3, d_4), and a zero dose (d_0) that served as the placebo control. The dosages were selected on the basis of results obtained from Phase I clinical trials conducted abroad.

Previous clinical trials had revealed the following. The investigational drug was promptly absorbed, distributed, metabolized, and excreted. A pharmacodynamic (PD) characteristic of this drug is that it induces the transient elevation of blood pressure, which might constitute a safety issue. Furthermore, the individual variability of the pharmacokinetic (PK) and PD parameters is high.

The management team responsible for conducting the trial in Japan had intended to plan a phase I clinical trial that was similar to the ones carried out overseas in order to compare PK and PD data between Japanese and foreign subjects. However, since this was the first administration of the investigational drug to Japanese subjects, the safety and tolerability of the subjects was the chief concern, and it was the elevation of blood pressure that was primarily evaluated.

Trial subjects were recruited from among the middle-aged and elderly female population, representative of the patients who typically suffer from SUI. One of the trial objectives was to estimate the mean values of PK parameters and blood pressure at each dosage as well as the differences between these among the dosages. And because of safety concern, it was necessary to administer the doses in ascending order from the lowest to the highest.

Initially, a crossover design had been considered because in the previous overseas trials it was found that the individual variability of the subjects could not be disregarded. However, most of the subjects were healthy housewives who did not work outside the home. Thus, the trial management team did not consider it feasible to ask the subjects to stay in a clinic for a few days. This is due to the fact that housewives in Japan are typically responsible for taking care of the family and performing all the daily household chores. Therefore, it is difficult for them to stay outside the home for a lengthy period of time.

Consequently, in order to reduce the subjects' stay at the clinic, the team had no choice but to follow a schedule in which each subject was administered a different dosage on two separate occasions only. Since it was essential to maintain a drug-free washout period of approximately two weeks between the first and second dosages, the enrolled subjects were randomly divided into two groups to shorten the duration of the trial.

Taking the above time considerations into account, the following schedule was adopted: the subjects in the first group were administered the investigational drug; during the washout period of the first group, those in the second group were administered the drug. Thus, the entire trial was conducted in four stages. This type of dosing schedule follows the alternating-panel rising

single dose (dose-ranging) crossover design proposed by Peace et al. (1998).

However, as mentioned previously, it was necessary to increase the dosage that the subjects received in a stepwise manner as follows: The subjects in the first group received the lowest dosage in the first stage. Next, provided there were no safety issues, the subjects in the second group received the second highest dosage in the second stage. Again, after ensuring the absence of any safety issues, those in the first group received the third highest dosage in the third stage. Finally, in the fourth stage, the highest dosage of the trial was administered in the same manner. To adequately evaluate safety, some subjects received a placebo in each stage.

Taking the above restrictions into account, the trial design shown in Table 1 was finally adopted. Note that there tended to be a slight imbalance in the number of subjects in the subgroups owing to the clinicians' requests for an equal number of subjects to be assigned to each dosage.

Table 1. Actual design adopted in the motivating case.

Group	Subjects	Period			
		t_1	t_2	t_3	t_4
G_1	3	d_0		d_3	
	2	d_1		d_0	
	3	d_1		d_2	
	3	d_1		d_3	
G_2	2		d_0		d_4
	2		d_1		d_4
	2		d_2		d_0
	2		d_2		d_3
	2		d_2		d_4

$d_0, d_1, \dots, d_4$ are doses in the ascending order.

3. Formulation of the problem for investigation

3.1 Formulation of the practical restrictions

To introduce our strategy, we formulate the situation in question into a slightly different form. The framework of the design in the motivating case was to devise two groups, with each group comprising four or five subgroups containing the same number of subjects. The objective of the present study, however, does not concern sample size determination but rather the identification of the optimal design under certain practical restrictions. We assume that each subgroup comprises a single subject, as shown in Table 2 in Section 4, because this allows us to capture the essential aspects of the optimal design in the present framework.

Consider the following conditions as restrictions.

*PR*₁: There are a total of five doses, $-d_0, d_1, \dots$, and d_4 ($d_0 < d_1 < \dots < d_4$) – of the investiga-

tional drug, where d_0 corresponds to the placebo.

*PR*₂: There are four dosing stages, i.e., t_1, t_2, t_3 , and t_4 ($t_1 < t_2 < t_3 < t_4$).

*PR*₃: There are eight subjects $I_1, I_2, \dots$, and I_8 who are randomly divided into two groups – G_1 and G_2 .

*PR*₄: The investigational drug is administered to subjects I_1, I_2, I_3 , and I_4 of group G_1 during the periods t_1 and t_3 , and to subjects I_5, I_6, I_7 , and I_8 of group G_2 during the periods t_2 and t_4 .

*PR*₅: The maximum dose is raised one level at each succeeding stage, i.e., d_j is the maximum dose at stage t_j ($j = 1, 2, 3, 4$), and at least one subject is given the maximum dose of each stage.

*PR*₆: At each stage, one subject receives the placebo.

In the motivating case, the restriction *PR*₅ was required by the clinicians, who were responsible for ensuring safety, while the restriction *PR*₆ was required by the trial management team to check for safety at each stage.

3.2 Statistical model

Consider the statistical model represented by Equation (1) for the response variables Y_{jk} ($j = 1, 2, 3, 4; k = 1, 2, \dots, 8$).

$$Y_{jk} = \mu + \alpha_i + \beta_j + \gamma_k + U_{jk}, \quad (1)$$

where Y_{jk} is the observed value of the response variable of the subject I_k at stage t_j , μ is the grand mean, α_i is the dose effect at d_i administered to subject I_k at t_j , β_j is the stage effect at t_j , γ_k is the subject effect of I_k , and U_{jk} s are random errors independently and normally distributed with mean 0 and variance σ^2 .

As per the objectives of this study, any pair of dose effects must be estimated, which is assured when all of $\alpha'_i = \{\alpha_i - \alpha_0; i = 1, 2, 3, 4\}$ are estimable. Although we are not interested in β s because they are nuisance parameters, we are inevitably forced to estimate them. Note that the dose d_i is automatically determined by the trial design once t_j and I_k are determined.

3.3 Reduction of the model

Under the above-mentioned restrictions, $\{Z_k = Y_{jk} - Y_{j'k}; k = 1, 2, \dots, 8\}$ constitutes the sufficient statistics for our framework and, therefore, the statistical model can be reduced to Equation (2) for $(Z_1, Z_2, \dots, Z_8)^t$ similar to Graßhoff and Schwabe (2003).

$$Z_k = (\alpha_i - \alpha_{i'}) + \beta_{jj'} + U_k \quad k = 1, 2, \dots, n, \quad (2)$$

where the superscript t denotes transpose, i and i' are the dose levels determined at (t_j, I_k) and $(t_{j'}, I_k)$, respectively, depending on the design, and $\beta_{jj'}$ is the difference of stage effects β_j and $\beta_{j'}$. Since the Y s are independent, the Z s are also independently and normally distributed with variance $2\sigma^2$.

Owing to the restriction PR_4 , the difference in stage effects for any subject in G_1 is $\beta_{13} = \beta_1 - \beta_3$, while that in G_2 is $\beta_{24} = \beta_2 - \beta_4$. In our study, the fact that the stage effects β_{13} and β_{24} are confounded with the group effects is not relevant because these stage effects as well as the group effects are regarded as nuisance parameters.

Since this model is a linear model, it can be expressed in matrix form as given in Equation (3).

$$\begin{pmatrix} Z_1 \\ Z_2 \\ \vdots \\ Z_8 \end{pmatrix} = \begin{pmatrix} x_{10} & x_{11} & \cdots & x_{14} & 1 & 0 \\ x_{20} & x_{21} & \cdots & x_{24} & 1 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ x_{40} & x_{41} & \cdots & x_{44} & 1 & 0 \\ x_{50} & x_{51} & \cdots & x_{54} & 0 & 1 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ x_{80} & x_{81} & \cdots & x_{84} & 0 & 1 \end{pmatrix} \begin{pmatrix} \alpha_0 \\ \alpha_1 \\ \alpha_2 \\ \alpha_3 \\ \alpha_4 \\ \beta_{13} \\ \beta_{24} \end{pmatrix} + \begin{pmatrix} U_1 \\ U_2 \\ \vdots \\ U_8 \end{pmatrix}, \quad (3)$$

where the x 's in each row of the 8×7 matrix specifies which two doses are administered sequentially to each subject. More precisely, x 's in any row are consist of one x takes the value of +1, one x the value of -1, and the remaining x 's the value 0s, leading the condition that the sum of the x 's in each row is 0. This signifies that the first column can be expressed as the sum of the succeeding four columns multiplied by -1, which enables us to reduce Equation (3) to Equation (4) without loss of generality.

$$\begin{pmatrix} Z_1 \\ Z_2 \\ \vdots \\ Z_8 \end{pmatrix} = \begin{pmatrix} x_{11} & x_{12} & \cdots & x_{14} & 1 & 0 \\ x_{21} & x_{22} & \cdots & x_{24} & 1 & 0 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ x_{41} & x_{42} & \cdots & x_{44} & 1 & 0 \\ x_{51} & x_{52} & \cdots & x_{54} & 0 & 1 \\ \vdots & \vdots & \ddots & \vdots & \vdots & \vdots \\ x_{81} & x_{82} & \cdots & x_{84} & 0 & 1 \end{pmatrix} \begin{pmatrix} \alpha'_1 \\ \alpha'_2 \\ \alpha'_3 \\ \alpha'_4 \\ \beta_{13} \\ \beta_{24} \end{pmatrix} + \begin{pmatrix} U_1 \\ U_2 \\ \vdots \\ U_8 \end{pmatrix} \quad (4)$$

Let X denote the 8×6 matrix on the right-hand side of Equation (4); then, the necessary and sufficient condition for estimability of all α s and β s is $\text{rank}(X) = 6$. We assume that this condition would be applicable throughout this paper.

3.4 Criteria for optimality

While the covariance matrix of the least squares estimator of the parameters in Equation (4) is uniquely defined as $2(X^t X)^{-1} \sigma^2$, our requirement is to minimize the variances corresponding to the 4×4 upper left submatrix.

We divide X into the four left columns, X_1 , and two right columns, X_2 . It follows that the covariance matrix for the least squares estimator of $(\alpha'_1 \alpha'_2 \alpha'_3 \alpha'_4)$ is given by $2Q\sigma^2$, where Q is defined by Equation (5) (Goos, 2002; Atkinson and Donev, 1992).

$$Q = (X_1^t X_1 - X_1^t X_2 (X_2^t X_2)^{-1} X_2^t X_1)^{-1} \quad (5)$$

Since $2\sigma^2$ is a fixed value, the problem lies in identifying the design that minimizes a scalar function of Q , which represents the volume of Q in some sense. According to the standard theory of the design of experiment, we shall consider the three scalars given below as indices of the volume.

1. $\det(Q)$ (determinant of Q)
2. $\text{trace}(Q)$ (sum of diagonal elements of Q)
3. $\max\{\text{diag}(Q)\}$ (maximum diagonal element of Q)

Among these three, $\det(Q)$ is proportional to the generalized variance, which is an index of dispersion of multivariate normal distribution of estimators. In Atkinson and Donev (1992), the minimization of this was referred to as the D_s -optimality (D -optimality for subset). When any contrasts in the dose effects is of interests in the experiment, we should use $\det(Q)$ as the criterion. Moreover, $\text{trace}(Q)$ represents the sum of variances of estimators, while $\max\{\text{diag}(Q)\}$ represents the worst variance of estimators. If the dose effects to placebo are our principal interest, we should use $\text{trace}(Q)$, whereas if we have to depress the maximum variance of the estimators, we should use $\max\{\text{diag}(Q)\}$.

4. Evaluation of the trial design

4.1 Enumeration algorithms for admissible designs

To establish an efficient enumeration algorithm, it is important to incorporate the given restrictions into the formulation of admissible designs. Taking the given restrictions stated earlier into consideration, we formulated that the admissible design will take the form shown in Table 2.

In Table 2, the fields containing any one of $d_0, d_1, \dots$ and d_4 are inevitably determined in the admissible designs. Needless to say, it is not necessary to differentiate between two or more designs derived from one design by exchanging the trial subjects. Without loss of generality, therefore, we can list the trial subjects in a lexical order with respect to the different doses.

For example, in stage t_1 , the highest dose is d_1 , while the lowest is d_0 , and only one subject receives d_0 . This means that in stage t_1 , subject I_1 receives dose d_0 , while I_2, I_3 and I_4 receive d_1 . Similarly, in stage t_2 , subject I_5 of group G_2 receives d_0 , while subject I_8 receives d_2 . Thus, in stage t_2 , only three different combinations, i.e., (d_1, d_1) , (d_1, d_2) and (d_2, d_2) , are admissible as doses of the remaining subjects I_6 and I_7 .

Table 2. Admissible design under the given restrictions.

Group	Subject	Period			
		t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_{31}	
	I_2	d_1		d_{32}	
	I_3	d_1		d_{33}	
	I_4	d_1		d_{34}	
G_2	I_5		d_0		d_{45}
	I_6		d_{26}		d_{46}
	I_7		d_{27}		d_{47}
	I_8		d_2		d_{48}

Doses with double subscripts are arbitrary if they satisfy the given restrictions.

In Table 2, the arbitrariness of the dose allocation is expressed by working variables d_{26} and d_{27} . In stages t_3 and t_4 , it is difficult to restrict the design in this manner. In order to determine the optimal design, we list, in lexical order, all possible cases for d_{jk} ($j = 3, 4$) and then eliminate the designs that do not satisfy abovementioned restrictions. That is, we eliminate the cases in which the maximum dose in stage t_j is not d_j , the number of subjects receiving d_0 in each period is not 1, or the rank of the design matrix is not 6. Using this enumeration algorithm, we can obtain all the admissible designs given the abovementioned restrictions.

4.2 Criteria values for admissible designs

When we listed out the admissible designs following the enumeration algorithm mentioned above, we obtained 2,805 designs for the case where 8 subjects are considered. The frequency distributions of the criteria values for all these designs are summarized in Fig.1 and Table 3.

Table 3. Summary statistics of optimality criteria for admissible designs.

Criterion	Minimum	Median	Mean	Maximum
$\det(Q)$	0.125	1.000	1.494	5.330
$\text{trace}(Q)$	3.188	6.100	7.008	30.000
$\max\{\text{diag}(Q)\}$	1.000	2.500	2.921	17.500

According to Fig.1 and Table 3, the criteria values show somewhat skewed distributions with long tails towards the right. In particular, some remarkably large values are realized for the criterion $\det(Q)$, which is relevant in this study. This implies the importance of evaluating the optimality of designs.

4.3 Optimal designs

Optimal designs that achieved the minimum criteria values are shown in Table 4 for $\det(Q)$, $\text{trace}(Q)$, and $\max\{\text{diag}(Q)\}$. In contrast, the worst designs that attained the maximum criteria

Fig. 1. Histogram of the optimality criteria for admissible designs.

values are shown in Table 5.

The dose allocation schedules in stages t_1 and t_2 are the same for these six designs. One of the characteristic features contrasting optimal designs with the worst designs is the combination of the first and second doses for the same subjects; many combinations of different doses appear in the optimal designs, while the same and limited combinations frequently appear in the worst designs.

The designs optimal for $\det(Q)$ and $\text{trace}(Q)$ are the same as is shown in Table 4 and the one for $\max(\text{diag}(Q))$ is quite similar to these two designs. Generally, the designs with small $\det(Q)$ were likely to have small $\text{trace}(Q)$ and vice versa.

Generally, in the clinical trials conducted at the initial stage of drug development, it would be desirable to estimate the differences in response among all the doses because an overall picture of the drug's action would be valuable. Furthermore, the D -optimality has an advantage in that it is invariant under any linear transformation of parameters. We, hereafter, mainly use $\det(Q)$ or D_s -optimality as the criterion for optimality.

For evaluation of the efficiency of a design, D -efficiency as defined by Equation (6) is fre-

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quently used.

$$D_{eff} = \left\{ \frac{\det(Q^*)}{\det(Q)} \right\}^{1/p}, \quad (6)$$

where Q^* in the numerator is the one that achieves the minimum $\det(Q)$ under the given restriction, Q in the denominator is the one in question, and p is the number of parameters. This is equivalent to the relative efficiency of an arbitrary design as compared with the optimum design in Atkinson and Denove (1992), and a value of D_{eff} that is less than 1 signifies the loss of efficiency. The relative efficiencies of the two designs located right side of Table 4 compared with that of the left side are 1.000 and 0.707, respectively (Goos, 2002; Atkinson, 1992). This signifies that a choice from the three optimality criteria does not have considerable influence on the choice of design in such a small trial as the motivating case.

Table 4. Optimal design minimizing the criteria $\det(Q)$, $\text{trace}(Q)$, and $\max\{\text{diag}(Q)\}$, respectively.

Criterion		$\det(Q)$				$\text{trace}(Q)$				$\det(Q)$			
Group	Subject	Period				Period				Period			
		t_1	t_2	t_3	t_4	t_1	t_2	t_3	t_4	t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_1		d_0		d_1		d_0		d_3	
	I_2	d_1		d_0		d_1		d_0		d_1		d_0	
	I_3	d_1		d_2		d_1		d_2		d_1		d_1	
	I_4	d_1		d_3		d_1		d_3		d_1		d_3	
G_2	I_5		d_0		d_3		d_0		d_3		d_0		d_4
	I_6		d_1		d_2		d_1		d_2		d_1		d_2
	I_7		d_1		d_4		d_1		d_4		d_1		d_4
	I_8		d_2		d_0		d_2		d_0		d_2		d_0

Table 5. Worst design maximizing the criteria $\det(Q)$, $\text{trace}(Q)$, and $\max\{\text{diag}(Q)\}$, respectively.

Criterion		$\det(Q)$				$\text{trace}(Q)$				$\det(Q)$			
Group	Subject	Period				Period				Period			
		t_1	t_2	t_3	t_4	t_1	t_2	t_3	t_4	t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_3		d_0		d_2		d_0		d_2	
	I_2	d_1		d_0		d_1		d_0		d_1		d_0	
	I_3	d_1		d_2		d_1		d_3		d_1		d_3	
	I_4	d_1		d_3		d_1		d_3		d_1		d_3	
G_2	I_5		d_0		d_0		d_0		d_3		d_0		d_3
	I_6		d_2		d_4		d_1		d_4		d_1		d_4
	I_7		d_2		d_4		d_1		d_4		d_1		d_4
	I_8		d_2		d_4		d_2		d_0		d_2		d_0

5. Nature of the optimal design

5.1 Number of subjects

Thus far, we have considered a number of subjects, i.e., eight subjects. To understand the nature of optimal designs, it is necessary to investigate whether the number of subjects has relevant influences on the characteristics of optimal designs. It is clear that a high number of subjects cannot be included in clinical pharmacology trials. Here, we examine the cases where the number of subjects is 6 or 10.

The number of admissible designs was 128 and 21,384 for 6 and 10 subjects, respectively. By calculating $\det(Q)$ for these designs, we could obtain D_s -optimal designs, which are presented in Table 6.

Table 6. Optimal design minimizing $\det(Q)$ in the cases of $n = 6$ and $n = 10$.

Group	$(n = 6)$ Subjects	Period				$(n = 10)$ Subjects	Period			
		t_1	t_2	t_3	t_4		t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_1		I_1	d_0		d_1	
	I_2	d_1		d_0		I_2	d_1		d_0	
	I_3	d_1		d_3		I_3	d_1		d_2	
						I_4	d_1		d_3	
						I_5	d_1		d_3	
G_2	I_4		d_0		d_4	I_6		d_0		d_3
	I_5		d_1		d_2	I_7		d_1		d_2
	I_6		d_2		d_0	I_8		d_1		d_4
						I_9		d_2		d_0
						I_{10}		d_2		d_4

The common features were identical to those in the case of $n = 8$. There was a relatively large number of dose combinations assigned to the same subjects and a large number of subjects were assigned to the minimum dose d_1 . Moreover, the designs with maximum $\det(Q)$ had the following characteristics; administrations of the same doses to the same subjects and more frequent assignments of relatively high dosages. The minimum dose d_1 appeared frequently because of the practical restriction of a stepwise increase of the dosage at each succeeding level. Furthermore, because of this restriction, it was unavoidable that the number of replications of the dosage, which was assigned to two stages, did not become the same within a group.

In actual cases, clinicians often request to keep the replication of all dosages same. There was only one case that corresponds to this requirement, whose $\det(Q)$ was 4.000, and its relative efficiency to the optimal design presented in Table 4 was as low as 0.420. The modification to reduce the disparity of the replication among the dosages should be considered in actual clinical trials taking into account the balance between the efficiency of design and the clinical advantage of this requirement.

5.2 Modification of the restrictions

In the optimal designs, the assignment frequency of the minimum dose d_1 was excessive, thus necessitating some modifications from the perspective of clinical interest. In order to address this issue, the following two approaches are considered.

To reduce the overall frequency of d_1 , the first approach is to assign – not including the placebo, which is to be administered at each stage – only doses d_2 and d_3 in stage t_3 and only doses d_3 and d_4 in stage t_4 . This is equivalent to selecting the trial designs that satisfy this new additional restriction from among a set of the designs obtained earlier – 267 designs were selected for $n = 8$. Naturally, the efficiency of the optimal designs under this additional restriction is less than that of the optimal designs under the original restrictions. However, such designs should be adopted if the loss of efficiency is not significant. The optimal design under the additional restriction is shown in Table 7. In this design, dose d_1 is administered four times; d_2 , four times; d_3 , twice, and d_4 , twice. Thus the difference among the dosages in terms of the number of replicates was considerably reduced. Further, since $\det(Q)$ of this design was 0.333 and D_{eff} as compared with the optimal design under the original restrictions was 0.783, the decrease in D_{eff} might be acceptable.

Table 7. Optimal design with restrictions on the repetition of low doses.

Group	Subject	Period			
		t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_2	
	I_2	d_1		d_0	
	I_3	d_1		d_2	
	I_4	d_1		d_3	
G_2	I_5		d_0		d_3
	I_6		d_1		d_4
	I_7		d_2		d_0
	I_8		d_2		d_4

The second approach is to assign more subjects in G_2 such that higher doses can be administered more easily than the subjects in G_1 . For example, if we derive the optimal design with three subjects in G_1 and five in G_2 , the design shown in Table 8 is obtained as the optimal design.

The frequency of doses d_2 , d_3 , and d_4 are in the range of 2 to 4. $\det(Q)$ of this design is 0.085, and its ratio (in the 4th root) to that of the optimal design under the original restrictions is 0.908. Approximately, a 10% reduction is achieved. We would recommend the second approach provided the capacity of the clinic allows the prescribed number of subjects in G_2 .

Table 8. Optimal design in the case with unequal group sizes.

Group	Subject	Period			
		t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_1	
	I_2	d_1		d_0	
	I_3	d_1		d_3	
G_2	I_4		d_0		d_2
	I_5		d_1		d_4
	I_6		d_2		d_0
	I_7		d_2		d_3
	I_8		d_2		d_4

5.3 Evaluation of the actual design

In this section, we evaluate the actual design in the motivating case. The design had a slight imbalance in terms of the number of subgroups and subjects in the subgroups, as shown in Table 1. In this evaluation, for simplicity, we assumed that each subgroup had one subject. We then listed the admissible designs with a total of nine subjects, with four subjects in the first group, G_1 , and five subjects in the second group, G_2 . The number of admissible designs was 11,765. The optimum design that minimized $\det(Q)$ is shown in Table 9, with $\det(Q)$ taking the value 0.063. For the actual design, $\det(Q)$ is 0.4 and D_{eff} is 0.631. Thus, the actual design had scope for improvement.

Table 9. Optimal design minimizing $\det(Q)$ ($n = 9$).

Group	Subject	Period			
		t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_1	
	I_2	d_1		d_0	
	I_3	d_1		d_2	
	I_4	d_1		d_3	
G_2	I_5		d_0		d_2
	I_6		d_1		d_4
	I_7		d_2		d_0
	I_8		d_2		d_3
	I_9		d_2		d_4

5.4 The case of ignorable period effects

The stage effect can be considered as the effect of environmental factors such as the air temperature or the food consumed by the subject. In some cases, however, it may be clear, in advance, that these factors do not have any effect. In such cases, because the stage effects β_{13} and β_{24} can be removed from the model given by Equation (4), the design matrix X becomes

Table 10. Optimal design in the case with negligible period effects.

Group	Subject	Period			
		t_1	t_2	t_3	t_4
G_1	I_1	d_0		d_3	
	I_2	d_1		d_0	
	I_3	d_1		d_2	
	I_4	d_1		d_3	
G_2	I_5		d_0		d_4
	I_6		d_1		d_4
	I_7		d_2		d_0
	I_8		d_2		d_3

equal to X_1 . Therefore the matrix Q is simply given by $Q = (X_1^t X_1)^{-1}$. Table 10 presents an optimal design under this condition. There is no major difference between the frequencies of doses in this design. This type of design should be adopted when the period effect is negligible.

6. Discussion

In actual clinical trials that are conducted at an early phase of drug development, trial statisticians are often required to accept various practical restrictions on the trial design. Although some of these restrictions may be strict, it may be possible to eliminate others through the trade-off relationship with efficiency loss.

In such situations, the choice of an appropriate dose allocation schedule together with the number of subjects poses problems for trial statisticians. They often adopt an intuitively plausible design without examining its optimality in detail, because appropriate references or examples that are directly applicable to the situation in question are unavailable.

The main purpose of this article is not to propose a novel method for designing clinical trials, but to show how the issues related to the design of clinical trials can be dealt with by using an actual case. The significance of the article lies in the fact that it provides a model that is directly applicable as a reference for trial statisticians who are faced with the abovementioned situation.

The methodological strategy the authors would like to propose is as follows:

- (1) Formulate the model on the primary endpoint as a fixed model or a mixed model with the fixed parameters to be estimated as accurately as possible.
- (2) Formulate the given restrictions on the design.
- (3) Determine the optimality criteria.
- (4) Enumerate all possible dosing schedules together with the number of subjects, using the algorithm that is as simple as possible under the given restrictions.

- (5) Evaluate the value of the optimality criteria for each design and identify the best design.
- (6) Examine the effect of modifying the restrictions and the advantage of the optimal design under the modified restrictions.
- (7) Fix the design to be adopted on the basis of both an impact of the efficiency loss and the practicability.

As mentioned in section 5.2, the frequency of minimum dosages is high in optimal designs. Two options are provided when the frequency of higher dosage needs to be increased.

If the clinic has adequate capacity, the approach that increases the number of subjects in the second group is recommended with regard to efficiency loss. However, if the capacity is inadequate, another approach can be chosen. Thus, a trial statistician can choose a reasonable approach by taking into account the balance between efficiency loss and feasibility. Moreover, as shown in section 5.3, the actual adopted design displayed considerable scope for improvement. This suggests that the abovementioned methodology is worth testing.

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REFERENCES

- Atkinson AC and Donev AN (1992). *Optimum Experimental Designs*. Clarendon Press, Oxford. (pp. 106–133.)
- Buoen C, Bjerrum OJ and Thomsen MS (2005). How First-Time-in-Human Studies Are Being Performed: A Survey of Phase I Dose-Escalation Trials in Healthy Volunteers Published Between 1995 and 2004. *J. Clin. Pharmacol.* **45**, 1123–1136.
- Goos P (2002). *The Optimal Design of Blocked and Split-Plot Experiments*. Springer, New York. (pp. 47–69.)
- Graßhoff U and Schwabe R (2003). On the analysis of paired observations. *Statistics and Probability Letters* **65**, 7–12.
- Haines LM, Perevozskaya I and Rosenberger WF (2003). Bayesian optimal designs for phase I clinical trials. *Biometrics* **59**, 591–600.
- Jones B and Kenward MG ed. (1989). *Design and Analysis of Cross-Over Trials*. Chapman & Hall, Tokyo. (pp. 189–211.)
- Ortega-Azurduy SA, Tan FES and Berger MPF (2008). The effect of dropout on the efficiency of D-optimal designs of linear mixed models. *Statistics in Medicine* **27**, 2601–2617.

- Peace KE ed. (1998). *Biopharmaceutical Statistics for Drug Development*. Marcel Dekker, New York and Basel. (pp. 273–288.)
- Tekle FB, Tan FES and Berger MPF (2008). D-optimal cohort designs for linear mixed-effects models. *Statistics in Medicine* **27**, 14, 2586–2600.
- Whitehead J and Zhou Y (2001). Easy-to-implement Bayesian methods for dose-escalation studies in healthy volunteers. *Biostatistics* **2**, 1, 47–61.
- Winkens B, Schouten HJA, Breukelen GJP and Berger MPF (2005). Optimal time-points in clinical trials with linearly divergent treatment effects. *Statistics in Medicine* **24**, 3743–3756.