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Compound Optimal Designs for Percentile Estimation in Dose-Response Models with Restricted Design Intervals

Compound Optimal Designs for Percentile Estimation in Dose-Response Models with Restricted Design Intervals

Stefanie Biedermann[1], Holger Dette[1], Wei Zhu[2]

Abstract

In dose-response studies, the dose range is often restricted due to ethics concerns over drug toxicity and/or efficacy, particularly when human subjects are involved. We present locally optimal designs for the estimation of several percentiles simultaneously on restricted as well as unrestricted design intervals. Our results are applicable to most of the commonly applied link functions with respect to the model under consideration. This work is a generalization of Dai (2000) where he showed that the same results hold for the logit model using Elfving's approach on trace optimal design (Elfving, 1952).

Keywords: Dose-response model; link function; percentile estimation; compound optimal design; A-optimality.

1 Introduction

We consider the common binary response model where a subject is administered a stimulus at a certain dose level x to study the relationship between the dose level and the probability $p = p(x)$ of a response. The response Y at dose level x is modeled as a binary random variable with success probability p, i.e. $Y \sim Bin(1, p)$. In this article, we deal with the following parametrization of a two parameter binary response model,

$$p(x) = F((x - \alpha)/\beta), \qquad \vartheta = (\alpha, \beta)^T, \ \alpha \in I\!R, \ \beta \in I\!R^+, \qquad (1)$$

where F denotes a known distribution function with density f. The Fisher information for the parameter ϑ of an observation at a dose level x is thus given by

$$I(z) = \frac{h^2(z)}{\beta^2} \begin{pmatrix} 1 & z \\ z & z^2 \end{pmatrix}, \quad z = \frac{x - \alpha}{\beta}, \qquad (2)$$

where $h^2(z) = f^2(z)/(F(z)(1 - F(z)))$. An approximate design ξ is a probability measure with finite support on $I\!R$ such that the observations are taken at the support points of ξ with frequencies proportional to the corresponding masses. The Fisher information matrix $M(\xi)$ of a design ξ is defined as the integral of $I(z)$ over the measure ξ, i.e.

$$M(\xi) = \int_{I\!R} I(z) \, d\xi(z), \qquad (3)$$

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and an optimal design minimizes a real-valued function $\Phi(\xi)$ of the inverse of the Fisher information matrix, which is usually referred to as an optimality criterion. In the framework of dose-response studies accomplished on human subjects such as clinical trials prior to the launch of new drugs, we often encounter the problem that the support points of an optimal design ξ with respect to some criterion function $\Phi(\cdot)$ lie outside a reasonable dosage range, i.e. Φ-optimal dose levels are either below zero or exceed safety levels such as the maximum tolerated dose of the drug. Practitioners are therefore in need of designs that take possibly restricted design intervals into account. In spite of an extensive amount of literature on optimal design for the binary response model on an unrestricted design space, so far there are relatively few articles concerning the topic of optimal design on restricted design spaces in this model. Extensive literature search yielded three related papers, one by Mats, Rosenberger and Flournoy (1998) where they derived the locally c- and D-optimal design for estimating the maximum tolerated dose in a Phase I clinical trial on a restricted design space, one by Haines, Perevozskaya and Rosenberger (2003) where they extend the latter approach to Bayesian c- and D-optimal designs and one by Biedermann, Dette and Zhu (2004), which deals with optimal designs with respect to a very general class of optimality criteria for the estimation of the vector of weighted parameters $(\sqrt{\lambda}\alpha, \sqrt{1-\lambda}\beta)^T$ on restricted and unrestricted design intervals.

In addition to estimating the model parameters of the underlying dose-response curve, there is also a great need to estimate other percentiles besides the median effective dose α. For example, the low percentiles are of particular interest in toxicity studies such as in virtually safe dose extrapolation studies, and the high percentiles are of interest in efficacy studies. The focus of this article is on the design situation where we try to estimate several percentiles simultaneously with different emphasis on the respective percentiles assuming that the corresponding design spaces are either unrestricted, one-side restricted or two-side restricted. The problem of optimal design for percentile estimation in dose-response experiments has first been addressed by Wu (1988) who derived designs that are optimal with respect to the estimation of one percentile at a time. This approach has been extended by several authors; see, e.g., a work of Zhu and Wong (2000) who focus on Bayesian optimal design for estimating the $ED50$ precisely, subject to the constraint that the efficiencies for estimating the other two quartiles $ED25$ and $ED75$ are not too low, or a recent work of Biedermann, Dette and Pepelyshev (2004) where model robust designs for percentile estimation in dose-response models are derived. The above authors, however, assume that the design interval comprises the entire real axis.

The organization of this article is as follows. In the first paragraph of section 2, the theoretical background is given and an appropriate optimality criterion for the problem of estimating several percentiles simultaneously is derived. We then apply results of Biedermann, Dette and Zhu (2004) to obtain the structure of the support of the optimal designs with respect to unrestricted, one-side restricted and two-side restricted design intervals. The next paragraph will be devoted to the derivation of the optimal weights utilizing a result of Pukelsheim and Torsney (1991). In section 3, finally, we will apply our results towards redesigning a dose

ranging trial of a new rheumatoid arthritis drug conducted at the Merck Research Laboratories (Zeng and Zhu, 1997). In this article, we are taking the Frequentists' approach (Chernoff, 1953) and thus our designs are termed "locally optimal". In the following, we will omit the word "locally" for simplicity.

2 Compound optimal designs for estimating several percentiles simultaneously

With parametrization (1), the $100p^{th}$ percentile Q_p of the underlying quantal response curve is given by

$$Q_p = ED100p = \beta \, F^{-1}(p) + \alpha. \tag{4}$$

As the maximum likelihood estimate $\hat{Q}_p$ for the $100p^{th}$ percentile, we therefore obtain

$$\hat{Q}_p = \hat{\beta} \, F^{-1}(p) + \hat{\alpha} \tag{5}$$

where $\hat{\alpha}$ and $\hat{\beta}$ denote the maximum likelihood estimators of α and β, respectively. If the goal is to design the experiment optimally for the estimation of one percentile Q_p at a time, it is thus reasonable to choose as optimality criterion to minimize the function

$$\varphi_p(\xi) = \mathrm{Var}(\hat{Q}_p) = \mathrm{Var}(\hat{\alpha}) + F^{-2}(p) \, \mathrm{Var}(\hat{\beta}) + 2F^{-1}(p) \, \mathrm{Cov}(\hat{\alpha}, \hat{\beta}), \tag{6}$$

i.e. to minimize the variance of the estimator $\hat{Q}_p$. If, in contrast, the experimenter's interest is in finding a good design for estimating several percentiles $Q_{p_1}, \ldots, Q_{p_k}$, $k \geq 2$, simultaneously, a reasonable choice of optimality criterion is the compound criterion $\Phi(\xi)$ where

$$\Phi(\xi) = \sum_{i=1}^{k} \lambda_i \, \varphi_{p_i}(\xi), \qquad \sum_{i=1}^{k} \lambda_i = 1, \tag{7}$$

i.e. $\Phi(\xi)$ minimizes a weighted average of the variances of the maximum likelihood estimators for the respective percentiles where the weights λ_i, $i = 1, \ldots, k$ are chosen accordingly with respect to the emphasis on the particular percentile Q_{p_i}, $i = 1, \ldots, k$. In practice, an even more general optimality criterion might be required if the precise estimation of an infinite number of percentiles Q_p is of interest, for example, when p is from some interval P, $P \subset [0, 1]$. Noting that

$$\begin{pmatrix} p_1 & \ldots & p_k \\ \lambda_1 & \ldots & \lambda_k \end{pmatrix}$$

describes a discrete probability measure on the unit interval $[0, 1]$, the compound criterion $\Phi(\xi)$ in (7) can be generalized by choosing an appropriate arbitrary distribution Λ with respect to p. We then obtain the generalized compound criterion

$$\Phi(\xi) = \int_0^1 \varphi_p(\xi) \, d\Lambda(p), \qquad \int_0^1 d\Lambda(p) = 1, \tag{8}$$

which is to be minimized with respect to the design ξ. Assume, for example, that the high percentiles from $Q_{0.9}$ to $Q_{0.95}$ are of equal interest in an efficacy study. Then a suitable choice for Λ would be the uniform distribution on the interval $[0.9, 0.95]$.

Since the variances of the percentile estimators can be of very different scale many authors (see, e.g., Dette, 1997) recommend the use of standardized optimality criteria. The above formulation of the criterion function (7) allows for this modification as follows. Assume that the aim is to minimize the standardized criterion

$$\tilde{\Phi}(\xi) = \sum_{i=1}^{k} \tilde{\lambda}_i \frac{\varphi_{p_i}(\xi)}{\varphi_{p_i}(\xi^*_{p_i})}$$

for a particular choice of weights $\tilde{\lambda}_i$, which add up to one, where $\xi^*_{p_i}$ denotes the optimal design for estimating the percentile Q_{p_i}. This is equivalent to minimizing (7) where the weights are given by

$$\lambda_i = \frac{\tilde{\lambda}_i}{\varphi_{p_i}(\xi^*_{p_i})} \Big/ \sum_{l=1}^{k} \frac{\tilde{\lambda}_l}{\varphi_{p_l}(\xi^*_{p_l})}, \qquad i = 1, \ldots, k$$

since the normalizing constant in the denominator of λ_i does not depend on ξ. A standardized version of the generalized compound criterion (8) can analogously be obtained by using a distribution Λ where

$$d\Lambda(p) = \frac{1}{\varphi_p(\xi^*_p)} d\tilde{\Lambda}(p) \Big/ \int_0^1 \frac{1}{\varphi_q(\xi^*_q)} d\tilde{\Lambda}(q)$$

and $\tilde{\Lambda}$ is a probability distribution with respect to p, which is chosen by the experimenter according to his emphasis on the particular percentiles. The designs ξ^*_p, $p \in [0, 1]$, are given in Wu (1988) so the distribution Λ can easily be obtained from $\tilde{\Lambda}$ and implemented in standard software such as Mathematica so that standardized optimal designs can be calculated in the same way as their non standardized counterparts.

A design ξ minimizing $\Phi(\cdot)$ in (7) is called a compound optimal design. Following Cook and Wong (1994), each compound optimal design is at the same time a constrained optimal design in the sense of Lee (1987), i.e. the individual criterion function φ_{p_j} for some $j \in \{1, \ldots, k\}$ is minimized subject to the constraints that the other percentiles are estimated with certain precisions. Solving the compound optimal design problem therefore also gives a solution to the constrained optimal design problem described above.

Since the compound criterion (7) is a special case of the generalized compound criterion (8) where Λ is a discrete distribution we will refer to the generalized criterion by $\Phi(\cdot)$ in the following. In the model framework of (1)-(3), we can rewrite the criterion function $\Phi(\xi)$ in terms of the Fisher information matrix

$$\Phi(\xi) = \mathrm{tr}(C^{-1}(\xi)), \quad C^{-1}(\xi) = K^T M^{-1}(\xi) K, \quad K = \begin{pmatrix} 1 & 0 \\ c_1 & \sqrt{c_2 - c_1^2} \end{pmatrix} \quad (9)$$

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where the expressions c_1 and c_2 are given by the first two moments of $F^{-1}(\cdot)$ with respect to the probability measure Λ, i.e.

$$c_1 = \int_0^1 F^{-1}(p)\, d\Lambda(p), \quad c_2 = \int_0^1 F^{-2}(p)\, d\Lambda(p).$$

A design ξ minimizing the criterion function $\Phi(\cdot)$ is therefore at the same time A-optimal for the estimation of the parameter vector $K^T \vartheta = (\alpha + c_1\beta, \sqrt{c_2 - c_1^2}\,\beta)^T$. We further note that the matrix $C(\xi)$ is also proportional to the Fisher information matrix for the parameter $K^T \tau$ in the linear regression model

$$y = \phi^T(z)\tau + \eta = \phi_1(z)\tau_1 + \phi_2(z)\tau_2 + \eta, \tag{10}$$

where $\phi_1(z) = h(z)/\beta$, $\phi_2(z) = h(z)(c_1 - z)/(\beta\sqrt{c_2 - c_1^2})$, τ_1 and τ_2 are model parameters and η is a normally distributed error with mean 0 and variance σ^2. Thus, the A-optimal design problem for estimating the parameter vector $(\alpha + c_1\beta, \sqrt{c_2 - c_1^2}\,\beta)^T$ in the binary response model coincides with an A-optimal design problem for the linear model (10).

In order to derive bounds on the number of support points of the Φ-optimal design ξ^* the following conditions on $h(\cdot)$ and thus the link function chosen to fit the binary response model (1) will be needed.

Condition (I): Let $g(z) = 1/h^2(z)$. Suppose that the function $g(\cdot)$ is twice differentiable on the entire real axis $\mathbb{R}$ and that the equation $g''(z) = c$ has at most two solutions for any real constant c.

Condition (II): $z \cdot h(z) \to 0$ as $z \to \pm\infty$.

Condition (I) is satisfied for most of the commonly applied link functions, such as the familiar logit and probit links as well as the asymmetrical complementary log-log and skewed logit link functions. The double exponential and double reciprocal links do not meet condition (I) due to their non-differentiability at the origin. Condition (II), in contrast, is complied with by all the above-mentioned link functions.

In the following lemma, we derive the number of support points of the Φ-optimal design ξ^* on any class of design intervals.

Lemma 1 *Assume that condition (I) is satisfied. Let the design interval $\mathcal{Z}$ be either unrestricted, one-side restricted or two-side restricted. Then the Φ-optimal design ξ^* with respect to any class for $\mathcal{Z}$ is supported on exactly two points, which are uniquely determined.*

We note that for any design space $\mathcal{Z}$, the Φ-optimal design ξ^* features exactly two points of support, thus leaving a three-dimensional minimization problem to solve. Theorem 1 summarizing the main results of this article gives further simplifications of this problem with respect to the position of the support.

Theorem 1 *Assume that conditions (I) and (II) are satisfied.*

(i) Let the design space be unrestricted, i.e. $\mathcal{Z} = \mathbb{R}$. If $h(\cdot)$ is symmetric and there is interest in estimating a set of percentiles symmetric about the $ED50$ with $\lambda_i = \lambda_j$ for $p_i = 1 - p_j$, i.e. $c_1 = 0$, the Φ-optimal design ξ^* with respect to $\mathcal{Z}$ is symmetric about zero with equal weights.

(ii) *Assume that the design interval $\mathcal{Z}$ is left-restricted, i.e. $\mathcal{Z} = [A, \infty)$, such that the lower support point of the Φ-optimal design ξ^* on the unrestricted design space is not included in $\mathcal{Z}$. Then the Φ-optimal design ξ_A^* with respect to the left-restricted design space $[A, \infty)$ has the boundary A as its lower support point. Analogously, for the right-restricted case $\mathcal{Z} = (-\infty, B]$ with the upper support point of the Φ-optimal design ξ^* on the unrestricted design space not included in $\mathcal{Z}$, we obtain that the upper support point of the Φ-optimal design ξ_B^* with respect to $(-\infty, B]$ is given by the boundary B.*

(iii) *Let the design interval be two-side restricted, i.e. $\mathcal{Z} = [A, B]$ with the upper support point of ξ_A^* and the lower support point of ξ_B^* not included in $\mathcal{Z}$. Then the support of the Φ-optimal design $\xi_{A,B}^*$ with respect to $\mathcal{Z} = [A, B]$ is given by the two ending points A and B.*

The proofs of Lemma 1 and Theorem 1 follow exactly the same lines as the corresponding proofs in Biedermann, Dette and Zhu (2004) for a more general class of optimality criteria and another matrix K and are therefore omitted.

From Theorem 1 it follows that in most cases, the three-dimensional minimization problem can be reduced to a one- or two-dimensional problem. In the subsequent paragraph, we derive a formula for the weights corresponding to the optimal design points, thus reducing the problem by a further dimension.

Denote the support points of the Φ-optimal design ξ^* with respect to some design interval $\mathcal{Z}$ by z_1 and z_2 where without loss of generality we assume that $z_1 < z_2$. The optimal weights ω_1 and ω_2 corresponding to z_1 and z_2 can then be derived from a result by Pukelsheim and Torsney (1991) as

$$\omega_1 = \frac{\sqrt{L_{11}}}{\sqrt{L_{11}} + \sqrt{L_{22}}} \quad \text{and} \quad \omega_2 = 1 - \omega_1 \tag{11}$$

where L_{ii}, $i = 1, 2$ are the diagonal elements of the non-negative definite 2×2 matrix $L = VV^T$ and $V = (XX^T)^{-1}XK$ with $X^T = (\phi(z_1), \phi(z_2)) \in \mathbb{R}^{2 \times 2}$. From

$$V = \frac{\beta}{z_2 - z_1} \begin{pmatrix} \frac{z_2 - c_1}{h(z_1)} & -\frac{\sqrt{c_2 - c_1^2}}{h(z_1)} \\ -\frac{z_1 - c_1}{h(z_2)} & \frac{\sqrt{c_2 - c_1^2}}{h(z_2)} \end{pmatrix} \tag{12}$$

and (11), it then follows that the optimal weight corresponding to the lower support point z_1 is given by

$$\omega_1 = \frac{\sqrt{\frac{z_2^2 - 2z_2 c_1 + c_2}{(z_2 - z_1)^2 h^2(z_1)}}}{\sqrt{\frac{z_2^2 - 2z_2 c_1 + c_2}{(z_2 - z_1)^2 h^2(z_1)}} + \sqrt{\frac{z_1^2 - 2z_1 c_1 + c_2}{(z_2 - z_1)^2 h^2(z_2)}}} . \tag{13}$$

In the two-side restricted case we thus obtain the optimal design ξ^* directly by plugging the boundary values A and B of the design interval into formula (13). If the design interval is one-side restricted or unrestricted, i.e. the support points of the optimal design ξ^* are not known in advance, plugging the weight formula (13) into the criterion function $\Phi(\xi)$ reduces the minimization problem by one

dimension. With the assertions of Lemma 1, Theorem 1 and (13), the design problem can easily be implemented in standard software such as Mathematica or Matlab so that the Φ-optimal design ξ^* with respect to any design interval $\mathcal{Z}$ can be calculated.

3   Examples: Merck Dose Ranging Trial Revisited

To show the practical relevance of our approach, we will reanalyze a real data example from the Merck Research Laboratories. Prior to a dose ranging trial on a new rheumatoid arthritis drug a pilot study including 120 patients was carried out where the study design was uniform on a placebo (dose 0) and a relatively high dose (dose 50). The response rates were 35% at the placebo dose and 65% at the high dose and the logit link was found to fit the data appropriately (Zeng and Zhu, 1997). The maximum likelihood estimates $\hat{\alpha}$ and $\hat{\beta}$ of the model parameters α and β are given by $\hat{\alpha} \approx 25$ and $\hat{\beta} \approx 40.3852$. Apart from the $ED50$, which is always of importance to estimate, a major dose of interest for the Merck dose ranging trial is the threshold dose or minimum clinically significant dose, which is defined as the dose level with 20% more responders than the placebo. From the pilot study, the threshold dose in this example is estimated to be $ED55$. However, since there are some uncertainties associated with the estimate, we estimate the threshold dose to be between $ED45$ and $ED65$. (The 95% confidence interval for the threshold dose based on the pilot study is $[ED46, ED64]$.) We therefore chose $Q_{0.45}$, $Q_{0.5}$ and $Q_{0.65}$ to be the percentiles of interest in the first example. The results of this compound optimal design problem are at the same time solutions to the corresponding constrained optimal design problem (Cook and Wong, 1994). In the second example we calculate generalized compound optimal designs for $\tilde{\Lambda}$ being the uniform distribution on the interval $[0.45, 0.65]$ plus some extra weight on $p = 0.5$. The third example, finally deals with a similar choice of $\tilde{\Lambda}$ where a triangular density with maximal value at $p = 0.55$ plus some extra weight at $p = 0.50$ is used, revealing the larger interest in $Q_{0.55}$ compared to $Q_{0.45}$ and $Q_{0.65}$. In all the examples above, we calculated designs with respect to the standardized criterion. For a more detailed discussion on the importance of estimating the threshold dose in rheumatoid arthritis studies and thus further motivation for our choice, see Zeng, Zhu and Wong (2000).

For the first example, we allocated various different weights $\tilde{\lambda}_i$, $i = 1, 2, 3$, to the three percentiles $Q_{0.45}$, $Q_{0.5}$ and $Q_{0.65}$. Table 1 shows the compound optimal designs with respect to these choices if there is no restriction on the design region. We observe from Table 1 that the optimal lower dose level x_1 is negative for all choices of $\tilde{\Lambda}$, i.e. the lower dose would have less drug content than the placebo. To avoid the negative dose levels we restricted the design interval to $[0, \infty)$ in terms of the original dosages. This translates to a normalized dose range of $[-0.6190, \infty)$. Selected left-restricted compound optimal designs in terms of the normalized as well as the original support points are displayed in Table 2.

As the larger support points x_2 from the left-restricted compound optimal designs appear to be relatively high, we felt the necessity to restrict the design interval

Table 1: Selected unrestricted compound optimal designs for estimating $Q_{0.45}$, $Q_{0.5}$ and $Q_{0.65}$ in terms of support points x_1, x_2 and normalized support points z_1, z_2

$\tilde{\lambda}_1$	$\tilde{\lambda}_2$	$\tilde{\lambda}_3$	z_1	z_2	x_1	x_2	ω_1	ω_2
0.33	0.34	0.33	-0.8116	0.8116	-7.777	57.755	0.4351	0.5649
0.25	0.5	0.25	-0.7619	0.7619	-5.769	55.748	0.4470	0.5530
0.4	0.2	0.4	-0.8474	0.8474	-9.224	59.201	0.4252	0.5748
0.5	0	0.5	-0.8904	0.8904	-10.958	60.934	0.4116	0.5884
0.33	0	0.67	-0.9041	0.9041	-11.514	61.489	0.3478	0.6522
0.67	0	0.33	-0.8455	0.8455	-9.146	59.123	0.4731	0.5269

Table 2: Selected left-restricted compound optimal designs for estimating $Q_{0.45}$, $Q_{0.5}$ and $Q_{0.65}$ in terms of support points x_1, x_2 and normalized support points z_1, z_2 on the original design interval $[0, \infty)$

$\tilde{\lambda}_1$	$\tilde{\lambda}_2$	$\tilde{\lambda}_3$	z_1	z_2	x_1	x_2	ω_1	ω_2
0.33	0.34	0.33	-0.6190	0.9714	0	64.231	0.5109	0.4891
0.25	0.5	0.25	-0.6190	0.8836	0	60.684	0.5104	0.4896
0.4	0.2	0.4	-0.6190	1.0316	0	66.660	0.5073	0.4927
0.5	0	0.5	-0.6190	1.0993	0	69.393	0.4986	0.5014
0.33	0	0.67	-0.6190	1.0726	0	68.317	0.4261	0.5739
0.67	0	0.33	-0.6190	1.0669	0	68.087	0.5612	0.4388

at both ends, obtaining the interval $[0, 60]$ in the original scale. The two-side restricted compound optimal designs are supported at the two ending points with corresponding allocation proportions shown in Table 3.

For the second example, we chose $\tilde{\Lambda}$ to allocate weight 0.8 to the uniform distribution on the interval $[0.45, 0.65]$ plus an extra weight of 0.2 to the single point $p = 0.5$. This choice corresponds to the goal of estimating $Q_{0.45}$–$Q_{0.65}$ equally well giving some extra emphasis to $Q_{0.5}$. If, however, the experimenter has more confidence in the initial estimates from the pilot study he might want to assign more weight to $p = 0.55$ compared to $p = 0.45$ and $p = 0.65$. To account for that,

Table 3: Selected two-side restricted compound optimal designs for estimating $Q_{0.45}$, $Q_{0.5}$ and $Q_{0.65}$ in terms of support points x_1, x_2 and normalized support points z_1, z_2 on the original design interval $[0, 60]$

$\tilde{\lambda}_1$	$\tilde{\lambda}_2$	$\tilde{\lambda}_3$	z_1	z_2	x_1	x_2	ω_1	ω_2
0.33	0.34	0.33	-0.6190	0.8667	0	60	0.4887	0.5113
0.25	0.5	0.25	-0.6190	0.8667	0	60	0.5065	0.4935
0.4	0.2	0.4	-0.6190	0.8667	0	60	0.4739	0.5261
0.5	0	0.5	-0.6190	0.8667	0	60	0.4540	0.5460
0.33	0	0.67	-0.6190	0.8667	0	60	0.3808	0.6192
0.67	0	0.33	-0.6190	0.8667	0	60	0.5258	0.4742

we chose $\tilde{\Lambda}$ allocating weight 0.8 to the distribution with triangular density

$$
f(p) = \begin{cases}
100(p - 0.45) & : & 0.45 \leq p \leq 0.55 \\
100(0.65 - p) & : & 0.55 < p \leq 0.65 \\
0 & : & \text{otherwise}
\end{cases}
$$

centered around $p = 0.55$ plus, again, an extra weight of 0.2 to the single point $p = 0.5$ as a third example. The compound optimal designs with respect to example 2 and example 3 are given in Table 4.

Table 4: Selected unrestricted and left-restricted compound optimal designs for estimating $Q_{0.45}$–$Q_{0.65}$ and $Q_{0.5}$ in terms of support points x_1, x_2 and normalized support points z_1, z_2

$\tilde{\Lambda}$	z_1	z_2	x_1	x_2	ω_1	ω_2
example 2	-0.6722	0.6722	-2.145	52.127	0.3950	0.6050
example 2 (left rest.)	-0.6190	0.7066	0	53.538	0.4198	0.5802
example 3	-0.5905	0.5906	1.149	48.835	0.3762	0.6238

In these two examples, there is less emphasis on the precise estimation of the "boundary" percentiles $Q_{0.45}$ and $Q_{0.65}$ than in the first example. The support points of the compound optimal designs are therefore less spread on the real axis. For example 2, there is still the necessity to restrict the design interval on the left side whereas for example 3, where the most interest is on the percentiles $Q_{0.5}$ and those "close to" $Q_{0.55}$ the design range needn't be restricted at all.

3.1 Finite sample performance of compound optimal designs

In order to study the benefits of compound optimal designs we used a simulation study and generated data according to the logit model

$$Y_i \sim Bin(1, p_i), \quad p_i = 1/(1 + e^{-(x_i - \alpha)/\beta}), \tag{14}$$

where $\alpha = 25$ and $\beta = 40.3852$. In this study, we compared 2 designs to evaluate how much we win by using the optimal design.

(1) The two-side restricted compound optimal design ξ_c^* for estimating $Q_{0.45}$, $Q_{0.5}$ and $Q_{0.65}$ with weights $\tilde{\lambda}_1 = 0.33$, $\tilde{\lambda}_2 = 0.34$, and $\tilde{\lambda}_3 = 0.33$ from the first example.

(2) The uniform design ξ_u^* on the five equidistant points $0, 15, 30, 45, 60$ from the interval $[0, 60]$ including the endpoints (placebo dose and highest dosage level).

We chose a uniform design as the competing design since equal allocation schemes are widely used in practice; see, e.g., Zhu, Ahn and Wong (1998). As it is unlikely that researchers will adopt an equal allocation rule with more than nine support points for estimating three different parameters we decided in favor of a five point design.

Table 5: Simulated mean squared errors of the maximum likelihood estimates $\hat{Q}_{0.45}$, $\hat{Q}_{0.5}$ and $\hat{Q}_{0.65}$ for the two different designs

	$n = 100$			$n = 200$			$n = 300$		
	$\hat{Q}_{0.45}$	$\hat{Q}_{0.5}$	$\hat{Q}_{0.65}$	$\hat{Q}_{0.45}$	$\hat{Q}_{0.5}$	$\hat{Q}_{0.65}$	$\hat{Q}_{0.45}$	$\hat{Q}_{0.5}$	$\hat{Q}_{0.65}$
ξ_c^*	125.17	99.35	168.72	49.97	43.73	65.75	32.52	27.00	42.05
ξ_u^*	239.19	251.77	2150.9	122.97	57.96	156.52	42.67	29.89	63.38

Table 5 shows the simulated mean squared error of the maximum likelihood estimates $\hat{Q}_{0.45}$, $\hat{Q}_{0.5}$ and $\hat{Q}_{0.65}$ based on data generated from model (14) with model parameters $\alpha = 25$, $\beta = 40.3852$. The sample sizes were given by 100, 200 and 300, respectively, and 10,000 runs were carried out. The above sample sizes were chosen consistently with the usual sample sizes in phase II clinical trials [see, e.g., www.clinicaltrials.gov/ct/info/phase for more information on sample sizes in clinical trials].

We observe substantial differences between the different designs, particularly when the sample size is small to moderate. The simulated mean squared errors for all percentiles turn out to be significantly larger if the data were generated according to the uniform design ξ_u^*. Consider, for example, the performance of the uniform design when the sample size is given by $n = 200$. Then $\hat{Q}_{0.45}$ and $\hat{Q}_{0.65}$ achieve

similar precisions as the corresponding estimates where data were collected according to the compound optimal design with only half the sample size, i.e. $n = 100$. For estimating the 50%-percentile $Q_{0.5}$ the loss in precision when collecting data according to the uniform design ξ_u^* is not so severe but still substantial. The use of the compound optimal design is therefore strongly recommended.

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