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

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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,

$$p(x) = F((x - \alpha)/\beta), \qquad \vartheta = (\alpha, \beta)^T, \ \alpha \in \mathbb{R}, \ \beta \in \mathbb{R}^+, \tag{1}$$

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

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

where $h^2(z) = f^2(z)/(F(z)(1 - F(z)))$. An approximate design ξ is a probability measure with finite support on $\mathbb{R}$ such that the observations are taken at the support points of ξ with frequencies proportional to the corresponding masses.

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The Fisher information matrix $M(\xi)$ of a design ξ is defined as the integral of $I(z)$ over the measure ξ, i.e.

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

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 (2006), 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 what follows, we will refer to a design interval $\mathcal{Z}$ of the form $[A, B]$ as two-sided restricted, $(-\infty, B]$ or $[A, \infty)$ as one-sided restricted and $\mathcal{Z} = \mathbb{R}$ as unrestricted where $A, B \in \mathbb{R}$.
Apart from estimating the model parameters of the underlying dose-response curve, there is also a great interest in estimating 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 designing experiments for the precise estimation of several percentiles simultaneously with different emphasis. We consider design spaces that are either unrestricted, one-sided restricted or two-sided 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 (2006) 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 the new geometric results of Biedermann, Dette and Zhu (2006) to obtain the structure of the support of the optimal designs. Subsequently, the optimal weights will be derived 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 variance of the estimator $\hat{Q}_p$, i.e.

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

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

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

$\Phi(\xi)$ is thus a weighted average of the variances of the maximum likelihood estimators for the respective percentiles where the weights $\lambda_i,\ i = 1, \ldots, k$, are chosen 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

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

where the weights $\tilde{\lambda}_i$ add up to one, and $\xi^*_{p_i}$ denotes the optimal design for estimating the percentile Q_{p_i}. This is equivalent to minimizing (7) or (8), respectively, where

$$\lambda_i = \frac{\tilde{\lambda}_i}{\varphi_{p_i}(\xi^*_{p_i})} \Big/ \sum_{l=1}^{k} \frac{\tilde{\lambda}_l}{\varphi_{p_l}(\xi^*_{p_l})}, \qquad d\Lambda(p) = \frac{1}{\varphi_p(\xi^*_p)}\, d\tilde{\Lambda}(p) \Big/ \int_0^1 \frac{1}{\varphi_q(\xi^*_q)}\, d\tilde{\Lambda}(q).$$

The designs ξ^*_p, $p \in [0,1]$, are given in Wu (1988) so the distribution Λ can easily be obtained from $\tilde{\Lambda}$ using standard software such as Mathematica.

Remark 1 *Note that the standardized criterion is in fact the inverse of the harmonic mean of the c_{p_i}-efficiencies, that is*

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

As pointed out in Dette (1997), standardization of the variances is essential because of the "different scales" of the functions φ_{p_i}. For a small quantile, say p_1, the variance of the estimate $\hat{\beta}$ dominates φ_{p_1}, and this expression will in turn dominate the values φ_{p_i} for moderate and larger quantiles p_i, $i \neq 1$. Consequently, if the criterion is not standardized and includes at least one "small" quantile, the optimal designs are "close" to the optimal design for estimating the slope, and do not take into account that other quantiles are of interest as well. The standardized criterion yields efficiencies, which are of the same size and therefore better comparable. For some numerical examples in a different context demonstrating the benefits of standardization see Dette and Sahm (1998).

In the model framework of (1)-(3), we can rewrite the criterion function $\Phi(\xi)$ in terms of the Fisher information matrix

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

where c_1 and c_2 are given by

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

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 $\phi_1\,(z) = h\,(z)\,/\beta$, $\phi_2\,(z) = h\,(z)\;(z - c_1)/(\beta\sqrt{c_2 - c_1^2})$, 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 $I\!R$ 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 satisfied 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 unrestricted, one-sided restricted and two-sided restricted design intervals $\mathcal{Z}$.

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

We note that for any design space $\mathcal{Z}$, the Φ-optimal design ξ^* has 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. $\mathcal{Z} = I\!R$. *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-sided 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 end points* A *and* B.

Since both proofs follow exactly the same lines as the corresponding proofs in Biedermann, Dette and Zhu (2006), only a brief outline of the proofs of Lemma 1 and Theorem 1, part (ii), will be given in what is to follow. From Theorem 1 in Biedermann, Dette and Zhu (2006), we learn that the Φ-optimal design problem is the dual problem of finding a centered ellipse $\mathcal{E}$ covering the induced design space $\mathcal{G} = \{\phi(z) = (\phi_1(z), \phi_2(z)) \mid z \in \mathcal{Z}\}$ (where ϕ_1, ϕ_2 are defined in (10)) with minimal v_1-content. $v_1(\mathcal{E})$ is by definition proportional to the volume of $\mathcal{E}$ divided by the L_1-norm of its diameters. From the points $\phi(z_i^*)$ where the ellipse $\mathcal{E}$ touches the induced design space $\mathcal{G}$ the support points z_i^* of the optimal design can be deduced. The proofs of Lemma 1 and Theorem 1 are based on the discussion how often this ellipse touches the induced design space. A centered ellipse $\mathcal{E}$ can be expressed in terms of a positive definite 2×2-matrix N as $\mathcal{E} = \{u \in I\!R^2 \mid u^T N u \leq 1\}$, and $\mathcal{E}$ contains $\mathcal{G}$ if and only if $\phi^T(z) N \phi(z) \leq 1$ for all $z \in \mathcal{Z}$. This is equivalent to $f(z) := az^2 + bz + c \leq h^{-2}(z) =: g(z)$ for all $z \in \mathcal{Z}$ and some real coefficients a, b and c. If there were three support points, i.e. points where $f(z) = g(z)$ we could find two points in between them where the derivatives of f and g are equal by the mean value theorem. Moreover, the support points are tangent points since $f(z) \leq g(z)$ for all z so that f and g have the same derivatives at these points as well. A further application of the mean value theorem to f' and g' then yields four points where the second derivatives $f''(z) = 2a$ and $g''(z)$ are equal, which contradicts with condition (I). To show that the end points of the restricted design intervals must be support points of the optimal design we consider exemplarily the case where $\mathcal{Z} = [B, \infty)$. First we notice that the Φ-optimal design ξ_B^* on the restricted design space $[B, \infty)$ satisfies $f(z) \leq h^{-2}(z)$ on the interval $[B, \infty)$ but not on the whole real axis from the uniqueness of the support of the unrestricted Φ-optimal design. Therefore there exists some $z' < B$ such that $f(z')h^2(z') > 1$. Moreover, from condition (II), it follows that there exists a point $z'' < z'$ such that for $z \leq z''$ the inequality $f(z)h^2(z) \leq 1$ holds again. Therefore we will encounter two intersection points z_0, z_1 between the functions $f(z)$ and $h^{-2}(z)$ on the interval $(-\infty, B]$. Assume that $z_0 < z_1 < B$ and denote by z_2, z_3 the support points of the design ξ_B^*, where $B < z_2 < z_3$, i.e. $f(z_i) = g(z_i)$ for $i = 0, 1, 2, 3$. By applying the mean value theorem to f and g and bearing in mind that z_2 and z_3 are tangent points, we obtain that there exist points z_1', $z_0 < z_1' < z_1 < B$ and z_2', $z_2 < z_2' < z_3$ with $f'(z_i') = g'(z_i')$, $i = 1, 2$ and $f'(z_i) = g'(z_i)$, $i = 2, 3$. A further application of the mean value theorem yields that there exist points z_i'', $i = 1, 2, 3$, $z_1' < z_1'' < z_2 < z_2'' < z_2' < z_3'' < z_3$ where $f''(z_i'') = g''(z_i'')$, $i = 1, 2, 3$, which leads to a contradiction with the fact that the equation $g''(z) = 2a$ can have at most two different solutions. Therefore, the smaller support point for the one-sided restricted Φ-optimal design must be the left boundary point of the design interval. To illustrate our results, we provide several figures displaying induced design spaces $\mathcal{G}$ with respect to different link functions and distributions Λ on p, as well as the corresponding covering ellipses with minimal v_1-content.

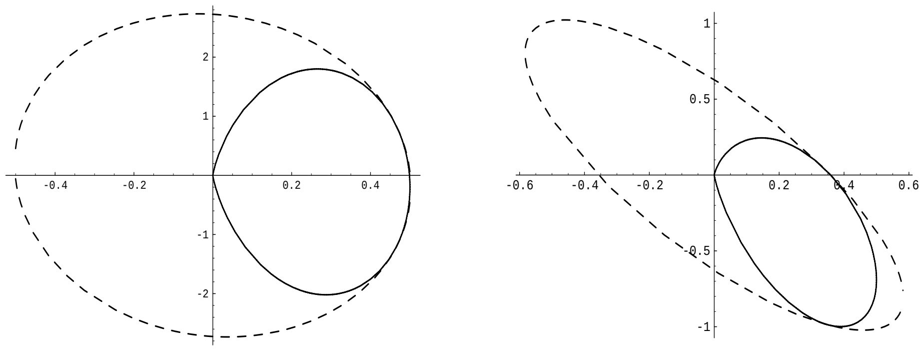
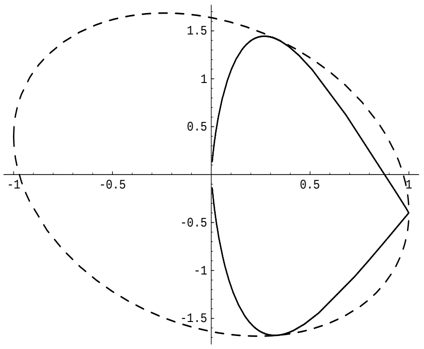


Figure 1: *The induced design space of the logit model with $\beta = 1$ (solid) and the corresponding optimal ellipse (dashed). Left part: $p_1 = 0.45$, $p_2 = 0.5$, $p_3 = 0.65$, $\lambda_1 = \lambda_3 = 0.33$, $\lambda_2 = 0.34$; Right part: $p_1 = 0.5$, $p_2 = 0.9$, $p_3 = 0.95$, $\lambda_1 = \lambda_3 = 0.33$, $\lambda_2 = 0.34$.*

Roughly speaking, the less symmetric the probability distribution Λ is about the $ED50$ the more skewed is the induced design space. This is reflected in Figures 1 and 2 where the induced design spaces on the respective left hand sides correspond to an almost symmetric Λ whereas the induced design spaces on the right hand sides have an underlying distribution Λ on p that is far from such symmetry.
However, it is obvious that for any Λ the induced design space of the logit model features such a shape that the centered covering ellipse $\mathcal{E}$ with minimal v_1-content touches $\mathcal{G}$ at exactly two points, which is in line with our result in Lemma 1. For the double exponential model, which does not satisfy condition (I), we find that the optimal ellipse $\mathcal{E}$ touches $\mathcal{G}$ at three points, so that the optimal designs for estimating several percentiles simultaneously will be supported at three different points if this link function is chosen.

From Theorem 1 it follows that in most cases, the three-dimensional minimiza-



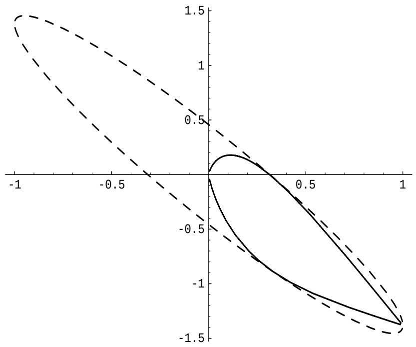


Figure 2: *The induced design space of the double exponential model with* $\beta = 1$ *(solid) and the corresponding optimal ellipse (dashed). Left part:* $p_1 = 0.45$, $p_2 = 0.5$, $p_3 = 0.65$, $\lambda_1 = \lambda_3 = 0.33$, $\lambda_2 = 0.34$*; Right part:* $p_1 = 0.5$, $p_2 = 0.9$, $p_3 = 0.95$, $\lambda_1 = \lambda_3 = 0.33$, $\lambda_2 = 0.34$.

tion problem can be reduced to a one- or two-dimensional problem. Applying the results of Pukelsheim and Torsney (1991) we find 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 $z_1 < z_2$. Then the optimal weight corresponding to the lower support point z_1 is given by

$$\omega_1 = \frac{\sqrt{\frac{z_2^2 - 2z_2c_1 + c_2}{(z_2-z_1)^2h^2(z_1)}}}{\sqrt{\frac{z_2^2 - 2z_2c_1 + c_2}{(z_2-z_1)^2h^2(z_1)}} + \sqrt{\frac{z_1^2 - 2z_1c_1 + c_2}{(z_2-z_1)^2h^2(z_2)}}}. \tag{11}$$

In the two-sided restricted case we thus obtain the optimal design ξ^* directly by plugging the boundary values A and B of the design interval into formula (11). If the design interval is one-sided restricted or unrestricted, substituting the weight formula (11) into the criterion function $\Phi(\xi)$ reduces the minimization problem by one dimension. With the assertions of Lemma 1, Theorem 1 and (11), the Φ-optimal design ξ^* with respect to any design interval $\mathcal{Z}$ can easily be found using standard software such as Mathematica or Matlab.

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. 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.

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

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 restricted the design interval at both ends to $[0, 60]$ in the original scale. The two-sided restricted compound optimal designs

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

are supported at the two end points with corresponding allocation proportions shown in Table 3.

Table 3: Selected two-sided 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

For the second example, we chose $\tilde{\Lambda}_2$ 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, we chose $\tilde{\Lambda}_3$ allocating weight 0.8 to the distribution with triangular density

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

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 $\tilde{\Lambda}_2$ and $\tilde{\Lambda}_3$ are given in Table 4.

Table 4: Unrestricted and left-restricted compound optimal designs for estimating $Q_{0.45}$–$Q_{0.65}$ and $Q_{0.5}$ with respect to $\tilde{\Lambda}_2$ and $\tilde{\Lambda}_3$ 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
$\tilde{\Lambda}_2$	-0.6722	0.6722	-2.145	52.127	0.3950	0.6050
$\tilde{\Lambda}_2$ (left rest.)	-0.6190	0.7066	0	53.538	0.4198	0.5802
$\tilde{\Lambda}_3$	-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.

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

$$Y_i \sim Bin(1, p_i), \quad p_i = 1/(1 + e^{-(x_i-\alpha)/\beta}), \tag{12}$$

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-sided 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 shows the simulated mean squared error of the maximum likelihood estimates $\hat{Q}_{0.45}$, $\hat{Q}_{0.5}$ and $\hat{Q}_{0.65}$. 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].

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

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.

Computer codes for calculating compound optimal designs will be sent to the reader on request, and optimal designs will also be available from the website http://www.optimal-design.org/optimal/Home.aspx in the near future.

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