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

Stefanie Biedermann\textsuperscript{1}, Holger Dette\textsuperscript{1}, Wei Zhu\textsuperscript{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,

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

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

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

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

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

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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 $\xi$ with respect to some criterion
function $\Phi(\cdot)$ lie outside a reasonable dosage range, i.e. $\Phi$-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 $\alpha$. 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 $ED_{50}$ precisely, subject to the con-
straint that the efficiencies for estimating the other two quartiles $ED_{25}$ and $ED_{75}$
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 100$^{th}$ percentile $Q_p$ of the underlying quantal response curve is given by

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

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

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

where $\hat{\alpha}$ and $\hat{\beta}$ denote the maximum likelihood estimators of $\alpha$ and $\beta$, 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

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

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

i.e. $\Phi(\xi)$ minimizes 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 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

$$\left(\begin{array}{c} p_1 \\ \lambda_1 \\ \vdots \\ p_k \\ \lambda_k \end{array}\right)$$

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 $\Lambda$ with respect to $p$. We then obtain the generalized compound criterion

$$\Phi(\xi) = \int_0^1 \varphi_p(\xi) \, d\Lambda(p), \hspace{1cm} \int_0^1 d\Lambda(p) = 1,$$ \hspace{1cm} (8)
which is to be minimized with respect to the design \( \xi \). 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 \( \Lambda \) 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 modi-
fication as follows. Assume that the aim is to minimize the standardized criterion
\[ \tilde{\Phi}(\xi) = \sum_{i=1}^{k} \tilde{\lambda}_i \frac{\varphi_{p_i}(\xi)}{\varphi_{p_i}(\xi^*_p)} \]
for a particular choice of weights \( \tilde{\lambda}_i \), which add up to one, where \( \xi^*_p \) denotes the
optimal design for estimating the percentile \( Q_{p_i} \). This is equivalent to minimizing
(7) where the weights are given by
\[ \lambda_i = \frac{\tilde{\lambda}_i}{\varphi_{p_i}([\xi^*_p])} \sum_{i=1}^{k} \frac{\tilde{\lambda}_i}{\varphi_{p_i}(\xi^*_p)}, \quad i = 1, \ldots, k \]
since the normalizing constant in the denominator of \( \lambda_i \) does not depend on \( \xi \). A
standardized version of the generalized compound criterion (8) can analogously be
obtained by using a distribution \( \Lambda \) where
\[ d\Lambda(p) = \frac{1}{\varphi_p(\xi^*_p)} d\tilde{\Lambda}(p) / \int_0^1 \frac{1}{\varphi_q(\xi^*_q)} d\tilde{\Lambda}(q) \]
and \( \tilde{\Lambda} \) is a probability distribution with respect to \( p \), which is chosen by the exper-
imenter according to his emphasis on the particular percentiles. The designs \( \xi^*_p \),
\( p \in [0, 1] \), are given in Wu (1988) so the distribution \( \Lambda \) can easily be obtained from
\( \tilde{\Lambda} \) and implemented in standard software such as Mathematica so that standard-
ized optimal designs can be calculated in the same way as their non standardized
counterparts.
A design \( \xi \) 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 \( \varphi_{p_j} \) 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 \( \Lambda \) 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
\[ \Phi(\xi) = \text{tr}(C^{-1}(\xi)), \quad C^{-1}(\xi) = K^T M^{-1}(\xi) K, \quad K = \begin{pmatrix} 1 & 0 \\ c_1 & \sqrt{c_2 - c_1^2} \end{pmatrix} \]
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 \( \Lambda \), 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 \( \xi \) minimizing the criterion function \( \Phi(\cdot) \) is therefore at the same time \( A \)-optimal for the estimation of the parameter vector \( K^T \theta = (\alpha + c_1 \beta, \sqrt{c_2 - c_1^2} \beta)^T \). 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 \( \phi_1(z) = h(z)/\beta, \phi_2(z) = h(z) (c_1 - z)/\beta \sqrt{c_2 - c_1^2} \) \( \tau_1 \) and \( \tau_2 \) are model parameters and \( \eta \) is a normally distributed error with mean 0 and variance \( \sigma^2 \).

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 \( \Phi \)-optimal design \( \xi^* \) 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):** \( z \cdot h(z) \rightarrow 0 \) as \( z \rightarrow \pm \infty \).

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 \( \Phi \)-optimal design \( \xi^* \) 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 \( \Phi \)-optimal design \( \xi^* \) 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 \( \Phi \)-optimal design \( \xi^* \) 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 \( \Phi \)-optimal design \( \xi^* \) with respect to \( \mathcal{Z} \) is symmetric about zero with equal weights.
(ii) Assume that the design interval $Z$ is left-restricted, i.e. $Z = [A, \infty)$, such that the lower support point of the $\Phi$-optimal design $\xi^*$ on the unrestricted design space is not included in $Z$. Then the $\Phi$-optimal design $\xi_\lambda$ 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 $Z = (-\infty, B]$ with the upper support point of the $\Phi$-optimal design $\xi^*$ on the unrestricted design space not included in $Z$, we obtain that the upper support point of the $\Phi$-optimal design $\xi_B^*$ with respect to $(-\infty, B]$ is given by the boundary $B$.

(iii) Let the design interval be two-side restricted, i.e. $Z = [A, B]$ with the upper support point of $\xi_A^*$ and the lower support point of $\xi_B^*$ not included in $Z$. Then the support of the $\Phi$-optimal design $\xi_{A,B}^*$ with respect to $Z = [A, B]$ 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 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 $\Phi$-optimal design $\xi^*$ with respect to some design interval $Z$ by $z_1$ and $z_2$ where without loss of generality we assume that $z_1 < z_2$. The optimal weights $\omega_1$ and $\omega_2$ corresponding to $z_1$ and $z_2$ can then be derived from a result by Pukelsheim and Torsney (1991) as

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

(11)

where $L_{ii}$, $i = 1, 2$ are the diagonal elements of the non-negative definite $2 \times 2$ 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

$$V = \frac{\beta}{z_2 - z_1} \left( \begin{array}{cc} \frac{z_2 - c_1}{h(z_1)} & -\sqrt{\frac{c_2 - c_1^2}{h(z_1)}} \\ -\frac{z_1 - c_1}{h(z_2)} & \sqrt{\frac{c_2 - c_1^2}{h(z_2)}} \end{array} \right)$$

(12)

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

$$\omega_1 = \frac{\sqrt{\frac{z_2^2 - 2z_2c_1 + c_1}{(z_2 - z_1)^2 h'(z_1)}}}{\sqrt{\frac{z_2^2 - 2z_2c_1 + c_1}{(z_2 - z_1)^2 h'(z_1)}} + \sqrt{\frac{z_1^2 - 2z_1c_1 + c_1}{(z_2 - z_1)^2 h'(z_2)}}}.$$  

(13)

In the two-side restricted case we thus obtain the optimal design $\xi^*$ 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 $\xi^*$ 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 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 ˆα and ˆβ of the model parameters
α and β are given by ˆα ≈ 25 and ˆβ ≈ 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
Q0.45, Q0.5 and Q0.65 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 Λ
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 Λ where
a triangular density with maximal value at p = 0.55 is used, revealing the larger interest in Q0.55 compared to Q0.45 and Q0.65.
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 ˆλi, i = 1, 2, 3, to the
three percentiles Q0.45, Q0.5 and Q0.65. 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 x1 is negative for all
choices of Λ, 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, ∞) in terms of
the original dosages. This translates to a normalized dose range of [−0.6190, ∞).
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 x2 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 $z_1$, $z_2$

<table>
<thead>
<tr>
<th>$\tilde{\lambda}_1$</th>
<th>$\tilde{\lambda}_2$</th>
<th>$\tilde{\lambda}_3$</th>
<th>$z_1$</th>
<th>$z_2$</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$\omega_1$</th>
<th>$\omega_2$</th>
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<tbody>
<tr>
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<td>-0.8116 0.8116 -7.777</td>
<td>57.755 0.4351 0.5649</td>
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<tr>
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<td>55.748 0.4470 0.5530</td>
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<td>59.201 0.4252 0.5748</td>
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<tr>
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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 $[0, \infty)$.

<table>
<thead>
<tr>
<th>$\tilde{\lambda}_1$</th>
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<th>$\tilde{\lambda}_3$</th>
<th>$z_1$</th>
<th>$z_2$</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$\omega_1$</th>
<th>$\omega_2$</th>
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<tbody>
<tr>
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<tr>
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<tr>
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<tr>
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<tr>
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<td>68.087 0.5612 0.4388</td>
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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 $\Lambda$ 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 $[0, 60]$.

<table>
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<tr>
<th>$\tilde{\lambda}_1$</th>
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<th>$\tilde{\lambda}_3$</th>
<th>$z_1$</th>
<th>$z_2$</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$\omega_1$</th>
<th>$\omega_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.33</td>
<td>0.34</td>
<td>0.33</td>
<td>-0.6190</td>
<td>0.8667</td>
<td>0</td>
<td>60</td>
<td>0.4887</td>
<td>0.5113</td>
</tr>
<tr>
<td>0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>-0.6190</td>
<td>0.8667</td>
<td>0</td>
<td>60</td>
<td>0.5065</td>
<td>0.4935</td>
</tr>
<tr>
<td>0.4</td>
<td>0.2</td>
<td>0.4</td>
<td>-0.6190</td>
<td>0.8667</td>
<td>0</td>
<td>60</td>
<td>0.4739</td>
<td>0.5261</td>
</tr>
<tr>
<td>0.5</td>
<td>0</td>
<td>0.5</td>
<td>-0.6190</td>
<td>0.8667</td>
<td>0</td>
<td>60</td>
<td>0.4540</td>
<td>0.5460</td>
</tr>
<tr>
<td>0.33</td>
<td>0</td>
<td>0.67</td>
<td>-0.6190</td>
<td>0.8667</td>
<td>0</td>
<td>60</td>
<td>0.3808</td>
<td>0.6192</td>
</tr>
<tr>
<td>0.67</td>
<td>0</td>
<td>0.33</td>
<td>-0.6190</td>
<td>0.8667</td>
<td>0</td>
<td>60</td>
<td>0.5258</td>
<td>0.4742</td>
</tr>
</tbody>
</table>

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 $z_1$, $z_2$.

<table>
<thead>
<tr>
<th>$\tilde{\Lambda}$</th>
<th>$z_1$</th>
<th>$z_2$</th>
<th>$x_1$</th>
<th>$x_2$</th>
<th>$\omega_1$</th>
<th>$\omega_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>example 2</td>
<td>-0.6722</td>
<td>0.6722</td>
<td>-2.145</td>
<td>52.127</td>
<td>0.3950</td>
<td>0.6050</td>
</tr>
<tr>
<td>example 2 (left rest.)</td>
<td>-0.6190</td>
<td>0.7066</td>
<td>0</td>
<td>53.538</td>
<td>0.4198</td>
<td>0.5802</td>
</tr>
<tr>
<td>example 3</td>
<td>-0.5905</td>
<td>0.5906</td>
<td>1.149</td>
<td>48.835</td>
<td>0.3762</td>
<td>0.6238</td>
</tr>
</tbody>
</table>

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

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

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 \( \xi^*_c \) 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 \( \xi^*_u \) 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

<table>
<thead>
<tr>
<th>( n )</th>
<th>( \hat{Q}_{0.45} )</th>
<th>( \hat{Q}_{0.5} )</th>
<th>( \hat{Q}_{0.65} )</th>
<th>( \hat{Q}_{0.45} )</th>
<th>( \hat{Q}_{0.5} )</th>
<th>( \hat{Q}_{0.65} )</th>
<th>( \hat{Q}_{0.45} )</th>
<th>( \hat{Q}_{0.5} )</th>
<th>( \hat{Q}_{0.65} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>200</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>125.17</td>
<td>99.35</td>
<td>168.72</td>
<td>49.97</td>
<td>43.73</td>
<td>65.75</td>
<td>32.52</td>
<td>27.00</td>
<td>42.05</td>
<td></td>
</tr>
<tr>
<td>239.19</td>
<td>251.77</td>
<td>2150.9</td>
<td>122.97</td>
<td>57.96</td>
<td>156.52</td>
<td>42.67</td>
<td>29.89</td>
<td>63.38</td>
<td></td>
</tr>
</tbody>
</table>

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 \( \xi^*_u \). 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 \( \xi_u^* \) is not so severe but still substantial. The use of the compound optimal design is therefore strongly recommended.

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**References**


