Optimal designs for dose finding studies

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Abstract

Identifying the "right" dose is one of the most critical and difficult steps in the clinical development process of any medicinal drug. Its importance cannot be understated: selecting too high a dose can result in unacceptable toxicity and associated safety problems, while choosing too low a dose leads to smaller chances of showing sufficient efficacy in confirmatory trials, thus reducing the chance of approval for the drug. In this paper we investigate the problem of deriving efficient designs for the estimation of the minimum effective dose (MED) by determining the appropriate number and actual levels of the doses to be administered to patients, as well as their relative sample size allocations. More specifically, we derive local optimal designs that minimize the asymptotic variance of the MED estimate under a particular dose response model. The small sample properties of these designs are investigated via simulation, together with their sensitivity to misspecification of the true parameter values and of the underlying dose response model. Finally, robust optimal designs are constructed, which take into account a set of potential dose response profiles within classes of models commonly used in practice.

Keywords and phrases: minimum effective dose, c-optimal design, dose response, Elfving's theorem

1 Introduction

Understanding and properly characterizing the dose response relationship is a fundamental step in the investigation of a compound, be it a new molecular entity, an environmental toxin, or an industrial chemical (Ruberg, 1995). Poor understanding of the dose response profile may have a direct impact on the estimation of a designated target dose level. In the context of pharmaceutical drug development, for example, selecting too high a dose can result in unacceptable toxicity, while choosing too low a dose decreases the chance of showing efficacy in the confirmatory phase, thus reducing the chance of getting regulatory approval for the drug. There are varying degrees of consequences associated with selecting a "wrong" dose level for a new compound. For example, it may be that only after having marketed a specified dose of a drug it becomes apparent that the level was set too high. This phenomenon has been documented by the U.S. Food and Drug Administration (FDA), who reported that approximately 10% of drugs approved between 1980-1989 have incurred dose changes - mostly decreases - of greater than 33% (Ruberg, 1995). Alternatively, the compound may fail regulatory approval due to an unacceptably high risk/benefit ratio. In such a setting two losses will result: (i) patients will never receive the incremental (or potentially ground-breaking) advancement in medical treatment and (ii) the missed opportunity will result in substantial financial losses for the pharmaceutical company who has developed the drug. The selection of the dose level(s) to be brought into the final confirmatory clinical studies, and hence for potential release on the market, is thus a key decision step involving inherent serious ethical and financial consequences.

In this paper we focus on the design of clinical dose finding studies aimed at estimating, efficiently and reliably, target dose(s) of interest within a dose range under investigation. For this purpose we will derive efficient designs for estimating the minimum effective dose (MED) which are robust with respect to the assumed dose response profile. Following Ruberg (1995), the MED is defined here as the "the smallest dose producing a clinically important response that can be declared statistically significantly different from the placebo response". This definition is consistent with international regulatory guidance documents, such as the ICH-E4 guideline (ICH, 1994), which describes one purpose of dose response information as identifying "the smallest dose with a discernible useful effect".

The rest of the paper is organized as follows. Section 2 introduces a motivating example from a real clinical dose finding study. Next, in Section 3, it is demonstrated that optimal design problems for MED-estimation are closely related to c-optimal design problems, which have been considered by several authors in the statistical literature (see Wu, 1988, Ford, Torsney and Wu, 1992, Pukelsheim, 1993, Chapter 2, Krewski, Smythe and Fung, 2002, Biedermann, Dette and Pepelyshev, 2006, among many others). Despite their limited practical applicability, we focus initially on local optimal designs (Chernoff, 1953), because they provide the foundation of the efficient robust designs described later in the text. In Section 4, we present local MED-optimal designs for commonly used dose response models. For many of those models, the optimal designs can be found explicitly using Elfving's (1952) well-known geometric characterization. The

sensitivity of local MED-optimal designs with respect to modeling assumptions is investigated in Section 5 and it shows that the performance of these designs is highly dependent on the agreement between the true and assumed dose response profiles. Because the true underlying dose response profile is typically unknown in practice, we derive, in Section 6, efficient designs which are robust to the model specification, using compound optimality criteria as introduced by Läuter (1974). It is shown that the derived designs have good properties for each of the models considered in our dose finding study. Finally, the Appendix contains some technical proofs of the theoretical results.

2 A motivating example

To illustrate and motivate the methods described in this paper we consider a real clinical dose finding study for an anti-anxiety drug (Pinheiro et al., 2006). The primary endpoint is the change in an anxiety scale score from baseline to the end of the study. A homoscedastic normal model is assumed. Without loss of generality it is also assumed that the average placebo effect is $f_0 = 0$ and the maximum treatment effect within the dose range $[\underline{x}, \overline{x}] = [0mg, 150mg]$ under investigation is $f_{\max} = 0.4$. Furthermore, we assume that all dose levels within the investigated dose range are safe, so that efficacy is the primary interest. The main goal of the study is to estimate the smallest dose level which produces at least the clinically relevant effect of $\Delta = 0.2$. Based on discussions with the clinical team prior to the start of the study, different candidate models were identified to potentially represent the true underlying dose response profile. These models characterize the prior uncertainty about the correct dose response shape. Table 1 shows these candidate models with guesstimates taken from previous studies as described in Pinheiro et al. (2006). The general expressions for these dose response models are given later in Section 3. Five of the models in Table 1 correspond to monotonically increasing dose response profiles, while the remaining models assume an umbrella shape allowing for a downturn in effect at higher dose levels. The corresponding curves are depicted in Figure 1.

The remaining key questions at the design stage involve the determination of the necessary number of different dose levels, the location of the dose levels within the dose range, and the proportions of patients to be allocated to each of the dose levels, such that the MED can be estimated efficiently for any of the candidate models. The original considerations for the example study led to a design with dose levels 0, 10, 25, 50, 100, and $150mg$ and a total sample size of 300 patients equally allocated to each of the six parallel treatment groups. Throughout this paper we call this the "standard design". Designs of this type will be improved substantially in this paper. For example, if the clinical team decides to have a design which is efficient for all models of Table 1, the resulting design using the methods described in this article would lead to 10% shorter confidence intervals for the MED as compared to the "standard design". This result holds for all models under consideration, except for the linear model, where there is essentially no difference in efficiency between the two designs. Furthermore, if the beta and the exponential models can be ruled out prior to the start of the study (because one believes in a monotonic

Table 1: *Dose response models with estimated parameters. All models are normalized such that the maximum effect is 0.4. For the first five models the maximum effect within the dose range under investigation is attained at the maximum dose level* $\bar{x} = 150mg$*, while for the beta models it is attained at* $x_{\max} = 25mg$ *and* $100mg$*, respectively.*

Model	$f(x, \vartheta)$
linear	$(0.4/150)x$
$E_{\max}$	$(7/15)x/(25+x)$
exponential	$0.08265(\exp(x/85) - 1)$
log-linear	$0.0797\log(x+1)$
logistic	$-0.004041 + 0.404082/\{1 + \exp((50-x)/10.88111)\}$
beta_1	$1.082(x/200)^{0.33}(1-x/200)^{2.31}$
beta_2	$2.747(x/200)^{1.39}(1-x/200)^{1.39}$

increase of effect characterized through a non-convex response curve, for example), the reduction of the confidence interval length is about 14% (for the $E_{\max}$) to 18% (for the logistic model). The gain in precision of the MED estimate can also be expressed in terms of sample sizes. In the last example, the standard design would require up to 44% more patients in order to estimate the MED with the same precision as the design proposed in this paper.

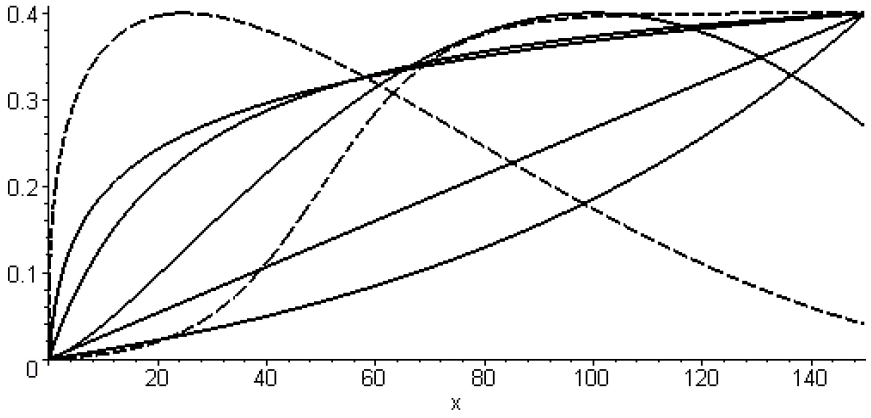

Figure 1: *The dose response curves corresponding to the models in Table 1.*

3 Optimal designs for the estimation of the MED

Consider the nonlinear regression model

$$Y_{ij} = f(x_i, \vartheta) + \varepsilon_{ij} = \vartheta_0 + \vartheta_1 f^0(x_i, \vartheta^0) + \varepsilon_{ij}, \quad i = 1, \ldots, k, \quad j = 1, \ldots, n_i, \tag{3.1}$$

where $\vartheta = (\vartheta_0, \vartheta_1, \vartheta^{0T})^T = (\vartheta_0, \ldots, \vartheta_p)^T$ denotes the unknown parameters, $\vartheta^{0T} = (\vartheta_2, \ldots, \vartheta_p)$, $x_1 < x_2 < \ldots < x_k$ denote the different dose levels and n_i denotes the number of patients treated with dose level x_i, $i = 1, \ldots, k$. If $\underline{x}$ denotes the placebo and $\overline{x}$ the maximum dose level, then the minimum effective dose (MED) is defined by

$$\text{MED} = \inf\{x \in (\underline{x}, \overline{x}] \mid f(\underline{x}, \vartheta) < f(x, \vartheta) - \Delta\},$$

where $\Delta > 0$ is the clinically relevant difference. Following Bretz et al. (2005), several possible estimates are available for evaluating the MED defined above, such as

$$\begin{aligned}
\widehat{\text{MED}}_1 &= \inf\{x \in (\underline{x}, \overline{x}] \mid U_x > f(\underline{x}, \hat{\vartheta}) + \Delta \ ; \ L_x > f(\underline{x}, \hat{\vartheta})\}, \\
\widehat{\text{MED}}_2 &= \inf\{x \in (\underline{x}, \overline{x}] \mid f(x, \hat{\vartheta}) > f(\underline{x}, \hat{\vartheta}) + \Delta \ ; \ L_x > f(\underline{x}, \hat{\vartheta})\}, \\
\widehat{\text{MED}}_3 &= \inf\{x \in (\underline{x}, \overline{x}] \mid L_x > f(\underline{x}, \hat{\vartheta}) + \Delta\},
\end{aligned}$$

where $\hat{\vartheta}$ is the least squares estimate of the parameter ϑ and L_x (U_x) is the lower (upper) bound of the confidence interval for $f(x, \vartheta)$. It is worthwhile to mention that for some values of Δ the estimates may not exist.

As shown below, for large sample sizes the variances of all three estimates have the same first order approximation used for the construction of "good" designs. Consequently, a MED-optimal design minimizes this approximation with respect to the choice of k (the number of different dose levels), $x_1, \ldots, x_k$ (the location of the dose levels) and $w_1, \ldots, w_k$ (the proportion of patients allocated to each dose level). Throughout this paper we consider approximate designs, which are defined as probability measures $\xi = \{x_i, w_i\}_{i=1}^k$ with finite support (Silvey, 1980; Pukelsheim, 1993). For a given design ξ and total sample size n the number of observations at each dose level is obtained by rounding the quantities nw_j to integers, such that $\sum_{j=1}^k n_j = n$ (Pukelsheim and Rieder, 1992).

From Seber and Wild (1989, p. 193) we obtain

$$L_x = f(x, \hat{\vartheta}) - u_{1-\alpha/2} \frac{\hat{\sigma}}{\sqrt{n}} \{g^T M^{-1}(\xi, \vartheta) g\}^{1/2} + o_P\Big(\frac{1}{\sqrt{n}}\Big) \ , \tag{3.2}$$

$$U_x = f(x, \hat{\vartheta}) + u_{1-\alpha/2} \frac{\hat{\sigma}}{\sqrt{n}} \{g^T M^{-1}(\xi, \vartheta) g\}^{1/2} + o_P\Big(\frac{1}{\sqrt{n}}\Big) \ , \tag{3.3}$$

for the upper and lower bound of the confidence interval for $f(x, \vartheta)$, where u_β denotes the β quantile of the standard normal distribution,

$$g^T = g^T(x, \vartheta) \ = \ \frac{\partial f(x, \vartheta)}{\partial \vartheta} = \Big(1, f^0(x, \vartheta^0), \vartheta_1 \frac{\partial f^0(x, \vartheta^0)}{\partial \vartheta_2}, \ldots, \vartheta_1 \frac{\partial f^0(x, \vartheta^0)}{\partial \vartheta_p}\Big) \in \mathbb{R}^{p+1} \tag{3.4}$$

is the gradient of the response function with respect to the parameter $\vartheta \in \mathbb{R}^{p+1}$, and

$$M(\xi, \vartheta) = \sum_{j=1}^{k} w_j g(x_j, \vartheta) g^T(x_j, \vartheta) \in \mathbb{R}^{p+1 \times p+1}$$

denotes the information matrix of the design ξ in the nonlinear regression model (3.1). In (3.2) and (3.3) the quantities $\hat{\sigma}^2$ and $\hat{\vartheta}$ are the common least squares estimates of σ^2 and ϑ, respectively (note that these estimates are asymptotically independent and normally distributed; see Seber and Wild, 1989, Theorem 2.1). Consequently, for a sufficiently large sample size we obtain as first order approximation for $\widehat{\text{MED}}_j$ $(j = 1, 2, 3)$

$$a_p(\hat{\vartheta}_0, \ldots, \hat{\vartheta}_p) := h^0\Big(f^0(\underline{x}, \hat{\vartheta}^0) + \frac{\Delta}{\hat{\vartheta}_1}\Big)$$

where $\hat{\vartheta}^0 = (\hat{\vartheta}_2, \ldots, \hat{\vartheta}_p)^T$ and h^0 denotes the inverse of the function f^0 with respect to the variable x. The δ-method (Van der Vaart, 1988) leads to

$$\begin{aligned} \text{Var}(\widehat{\text{MED}}_j) &= \text{Var}(a_p(\hat{\vartheta}_0, \ldots, \hat{\vartheta}_p)) + o_P(\frac{1}{n}) \\ &= \frac{\sigma^2}{n} b^T(\hat{\vartheta}_0, \ldots, \hat{\vartheta}_p) M^-(\xi, \hat{\vartheta}) b(\hat{\vartheta}_0, \ldots, \hat{\vartheta}_p) + o_P(\frac{1}{n}) \end{aligned} \tag{3.5}$$

for the asymptotic variance of the estimates for the MED_j, $j = 1, 2, 3$, where

$$b(\vartheta) = b(\vartheta_0, \ldots, \vartheta_p) = \frac{\partial}{\partial \vartheta} a(\vartheta_0, \ldots, \vartheta_p) = \frac{\partial}{\partial \vartheta} h^0\Big(f^0(\underline{x}, \vartheta^0) + \frac{\Delta}{\vartheta_1}\Big) \tag{3.6}$$

denotes the gradient of the function a with respect to ϑ. In (3.5) the matrix $M^-(\xi, \vartheta)$ denotes a generalized inverse of the matrix $M(\xi, \vartheta)$ and it is assumed that the MED is estimable by the design ξ, that is $\text{Range}(b(\vartheta)) \subset \text{Range}(M(\xi, \vartheta))$ (Pukelsheim, 1993, Chapter 3). Consequently, we call a design $\xi^*(\vartheta)$ local MED-optimal if it minimizes

$$\Psi(\xi) = b^T(\vartheta_0, \ldots, \vartheta_p) M^-(\xi, \vartheta) b(\vartheta_0, \ldots, \vartheta_p), \tag{3.7}$$

among all designs for which the MED is estimable. Boundaries for an (asymptotic) confidence interval for the MED are given by $\widehat{\text{MED}}_j \pm u_{1-\alpha/2} \hat{\sigma} \Psi(\xi)/\sqrt{n}$ and consequently the local MED-optimal design minimizes the (first order approximation of the) length of this interval. Note that the estimation of the MED does not require the estimation of all parameters in the model and as a consequence designs with singular information matrix are also of interest, which explains the use of a generalized inverse in (3.7). In fact many of the local MED-optimal designs derived in the following section will have a singular information matrix. Note also that the local MED-optimal design depends on the response function (more precisely on the function f^0) and on the unknown parameter ϑ. As discussed in Section 1, prior information for ϑ is often available in

pharmaceutical development. In the following we derive local MED-optimal designs for classes of dose response models commonly used in practice (Ratkowsky, 1989; Pinheiro et al., 2006):

$$f(x,\vartheta) = \vartheta_0 + \vartheta_1 x \qquad \text{linear} \tag{3.8}$$

$$f(x,\vartheta) = \vartheta_0 + \tfrac{\vartheta_1 x}{x+\vartheta_2} \qquad E_{\max} \tag{3.9}$$

$$f(x,\vartheta) = \vartheta_0 + \vartheta_1 \exp(x/\vartheta_2) \qquad \text{exponential} \tag{3.10}$$

$$f(x,\vartheta) = \vartheta_0 + \vartheta_1 \log(x+\vartheta_2) \qquad \text{log-linear} \tag{3.11}$$

$$f(x,\vartheta) = \vartheta_0 + \vartheta_1 (1+\exp((\vartheta_2 - x)/\vartheta_3))^{-1} \qquad \text{logistic} \tag{3.12}$$

$$f(x,\vartheta) = \vartheta_0 + \vartheta_1 B(\vartheta_2,\vartheta_3)(x/\vartheta_4)^{\vartheta_2}(1-x/\vartheta_4)^{\vartheta_3} \qquad \text{beta} \tag{3.13}$$

where $B(\vartheta_2,\vartheta_3) = (\vartheta_2/(\vartheta_2+\vartheta_3))^{-\vartheta_2}(\vartheta_3/(\vartheta_2+\vartheta_3))^{-\vartheta_3}$. Note that the function f in the beta model (3.13) is normalized such that the value $\vartheta_0+\vartheta_1$ corresponds to the maximum of the dose response function (which is attained at $\vartheta_* = \vartheta_2\vartheta_4/(\vartheta_2+\vartheta_3)$). The parameter ϑ_4 corresponds to the dose level above which there is no beneficial effect of the drug and we assume it to be fixed. Note that ϑ_4 can also be treated as a parameter to be estimated. For the sake of brevity we do not consider optimal designs for this alternative model. Instead, we derive in Section 4 local MED-optimal design for the dose response models (3.8) - (3.13) and apply those to the parameter values listed in Table 1. In Section 5 we investigate the sensitivity of the local MED-optimal designs with respect to misspecification of the parameter ϑ and the underlying function f in (3.1).

4 Local MED-optimal designs for a given functional form

We start considering the simpler models (3.8) - (3.11) and derive a theoretical result, which gives some insight into the general structure of the optimal designs for these models. The proof is given in the Appendix.

Theorem 4.1. *For the models (3.8) - (3.11) the local MED-optimal design depends only on the parameters Δ/ϑ_1 and ϑ_2. The local MED-optimal design is either (i) a two point design with equal weights at placebo $x_1 = \underline{x}$ and a second dose level x_2 depending on Δ/ϑ_1 and ϑ_2, or (ii) a three point design with weights $w, 0.5-w, 0.5$ at placebo $x_1 = \underline{x}$, the maximum dose level $x_3 = \bar{x}$ and a third dose $x_2 \in (\underline{x}, \overline{x})$ depending only on ϑ_2. Moreover, the weight $w \in (0, 0.5)$ depends on Δ/ϑ_1 and ϑ_2.*

Remark 4.2. Theorem 4.1 shows that local MED-optimal designs for the models (3.8) - (3.11) advise the experimenter to take observations at only 2 or 3 different dose levels. Moreover, it follows from the results of Section 8.3 in Pukelsheim (1993) that there always exists a local MED-optimal design for the models (3.12) and (3.13) with at most 4 different dose levels. Our numerical results indicate that for the logistic model (3.12) and for the beta model (3.13) local MED-optimal designs advise the experimenter to take observations at either 2 or 4 different dose levels.

4.1 Explicit solutions

For the response functions (3.8) - (3.11) the local MED-optimal designs can be determined explicitly and the results are summarized in the following two theorems.

Theorem 4.3.

(a) *For the linear model (3.8) the local MED-optimal design has equal weights at placebo* $x_1 = \underline{x}$ *and the maximum dose level* $x_2 = \bar{x}$.

(b) *Define* $r = \Delta/\vartheta_1$ *and* $\Delta^* = \vartheta_1\vartheta_2(\overline{x} - \underline{x})/\{2(\underline{x} + \vartheta_2)(\overline{x} + \vartheta_2)\}$. *If* $\Delta > \Delta^*$, *then the local MED-optimal design for the* $E_{\max}$ *model (3.9) is a two-point design with equal weights at placebo* $x_1 = \underline{x}$ *and the dose level*

$$x_2 = a_2(\vartheta_0, \vartheta_1, \vartheta_2) = \frac{\vartheta_2(r\vartheta_2 + (r+1)\underline{x})}{\vartheta_2 - r(\underline{x} + \vartheta_2)}.$$

If $\Delta < \Delta^*$, *then the local MED-optimal design is a three-point design with weights* $w, 0.5-w$ *and* 0.5 *at placebo* $x_1 = \underline{x}$, *the maximum dose level* $x_3 = \bar{x}$ *and the dose level*

$$x_2 = \frac{\overline{x}(\underline{x} + \vartheta_2) + \underline{x}(\overline{x} + \vartheta_2)}{(\underline{x} + \vartheta_2) + (\overline{x} + \vartheta_2)}, \tag{4.1}$$

where the weight w *is defined by*

$$w = \frac{1}{4} - \frac{1}{8}\frac{(\overline{x} - \underline{x})\vartheta_2}{(\underline{x} - \overline{x})\vartheta_2 + (\underline{x} + \overline{x})r\vartheta_2 + (\underline{x}\overline{x} + \vartheta_2^2)r}. \tag{4.2}$$

Example 4.4. In Table 2 we display some local MED-optimal designs for the $E_{\max}$ model based on the information from Section 2. The dose range is given by $[\underline{x}, \bar{x}] = [0mg, 150mg]$, the clinically relevant difference is $\Delta = 0.2$, and the guesstimates for the parameter ϑ are given by $\vartheta_1 = 0.4667$, $\vartheta_2 = 25$. We also calculate local MED-optimal designs for other values of the parameters Δ, ϑ_1, and ϑ_2 in order to study their influence on the optimal design. For example, if $\Delta = 0.1$, $\vartheta_1 = 0.4667$, and $\vartheta_2 = 25$ the local MED-optimal designs has weights 0.417, 0.5, and 0.083 at the points 0, 18.75, and $150mg$, respectively. That is, one is advised to consider the three dose levels 0, 18.75, and $150mg$, and allocate 41.7%, 50%, and 8.3% of the patients at these dose levels.

Let $\xi^*(\vartheta)$ denote the local MED-optimal design for given Δ and ϑ. Let ξ_s further denote the standard design actually being used in the example study with the six dose levels $0, 10, 25, 50, 100,$ and $150mg$. The last column of Table 2 shows the efficiency

$$\text{eff}(\xi_s) = \frac{\Psi(\xi^*(\vartheta))}{\Psi(\xi_s)}. \tag{4.3}$$

of the standard design ξ_s relative to the local MED-optimal designs ξ^*, where $\Psi(\xi)$ is defined in (3.7). We observe, that the standard design has approximately $45\% - 50\%$ efficiency in all

cases. That is, if the $E_{\max}$ model with the assumed parameter values was the true dose response model, then the use of the local MED-optimal design would need only about half of the number of patients required for the standard design to estimate the MED with the same precision. In other words, the local MED-optimal design would lead to 30% shorter confidence intervals for the MED as compared to the intervals obtained from the standard ξ_s actually being used in the study.

Table 2: *Local MED-optimal designs for the $E_{\max}$ model for various parameters. The dose range is the interval $[0mg, 150mg]$. The table also shows the efficiency of the standard design ξ_s.*

Δ	ϑ_1	ϑ_2	x_1	x_2	x_3	w_1	w_2	w_3	eff(ξ_s)
0.2	0.4667	15	0	11.25		0.5	0.5		0.4714
0.2	0.4667	25	0	18.75		0.5	0.5		0.4545
0.2	0.4667	35	0	26.25		0.5	0.5		0.4400
0.1	0.4667	25	0	18.75	150	0.417	0.5	0.083	0.5341
0.3	0.4667	25	0	45.00		0.5	0.5		0.4595
0.2	0.2667	25	0	74.96		0.5	0.5		0.5078
0.2	0.6667	25	0	18.75	150	0.442	0.5	0.058	0.5099

Theorem 4.5.

(a) *Define $r = \Delta/\vartheta_1$,*

$$x^* = \frac{(\overline{x} - \vartheta_2)e^{\overline{x}/\vartheta_2} - (\underline{x} - \vartheta_2)e^{\underline{x}/\vartheta_2}}{e^{\overline{x}/\vartheta_2} - e^{\underline{x}/\vartheta_2}},$$

$$w = \frac{1}{2}\frac{r(\overline{x}e^{\overline{x}/\vartheta_2} - x^*e^{x^*/\vartheta_2}) - (e^{\overline{x}/\vartheta_2} - e^{x^*/\vartheta_2})(\underline{x}e^{\underline{x}/\vartheta_2} - \vartheta_2(e^{\underline{x}/\vartheta_2} + r)\log(e^{\underline{x}/\vartheta_2} + r))}{r(\overline{x}e^{\overline{x}/\vartheta_2} - \underline{x}e^{\underline{x}/\vartheta_2}) - (e^{\overline{x}/\vartheta_2} - e^{\underline{x}/\vartheta_2})(\underline{x}e^{\underline{x}/\vartheta_2} - \vartheta_2(e^{\underline{x}/\vartheta_2} + r)\log(e^{\underline{x}/\vartheta_2} + r))}. \tag{4.4}$$

If $w \geq 0.5$, then the local MED-optimal design for the exponential model (3.10) is a two-point design with equal weights at placebo $x_1 = \underline{x}$ and the dose level

$$x_2 = a_2(\vartheta_0, \vartheta_1, \vartheta_2) = \vartheta_2 \log\Big\{\exp\Big(\frac{\underline{x}}{\vartheta_2}\Big) + r\Big\}.$$

If $w < 0.5$, then the local MED-optimal design ξ^* is a three-point design with weights w, $0.5 - w$ and 0.5 at placebo $x_1 = \underline{x}$, the maximum dose level $x_3 = \bar{x}$ and the dose level $x_2 = x^*$, where w and x^* are defined in (4.4).

(b) *Define $r = \Delta/\vartheta_1$,*

$$x^* = (\overline{x} + \vartheta_2)(\underline{x} + \vartheta_2)\frac{\log(\underline{x} + \vartheta_2) - \log(\overline{x} + \vartheta_2)}{\overline{x} - \underline{x}} + \vartheta_2,$$

(4.5)

$$w = \frac{1}{2} - \frac{1}{2}\frac{(e^r-1)\log\frac{x^*+\vartheta_2}{\underline{x}+\vartheta_2} + re^r\left(\frac{\underline{x}+\vartheta_2}{x^*+\vartheta_2}-1\right)}{(e^r-1)\log\frac{\bar{x}+\vartheta_2}{\underline{x}+\vartheta_2} + re^r\left(\frac{\underline{x}+\vartheta_2}{\bar{x}+\vartheta_2}-1\right)}.$$

If $w \geq 0.5$, then the local MED-optimal design for the log-linear model (3.11) is a two-point design with equal weights at placebo $x_1 = \underline{x}$ and the dose level

$$x_2 = a_2(\vartheta_0, \vartheta_1, \vartheta_2) = (\underline{x} + \vartheta_2)e^r - \vartheta_2.$$

If $w < 0.5$, then the local MED-optimal design has three points with weights w, $0.5 - w$ and 0.5 at placebo $x_1 = \underline{x}$, the maximum dose level $x_3 = \bar{x}$ and the dose level $x_2 = x^*$, where w and x^* are defined in (4.5).

Example 4.6. In Table 3 we display several local MED-optimal designs for the exponential model and the log-linear model based on the information from Section 2. In most cases the local optimal designs are two point designs and the efficiency of the standard design ξ_s is about 50% or less. The standard design would thus again require the double number of patients than the local optimal designs to estimate the MED with the same precision.

4.2 Numerical solutions

For the logistic model (3.12) and the beta model (3.13) analytical solutions for the local MED-optimal design problem are not available and numerical methods have to be used for the calculation of the optimal designs. We assume that the parameter ϑ_4 in the beta model is fixed and given by 200, with the interpretation that this is the dose level above which no beneficial effect of the drug over placebo is expected. Local MED-optimal designs in the situation, where ϑ_4 is also estimated from the data, lead to similar results and are available from the authors.
For the logistic and the beta model our numerical results indicate two types of local MED-optimal designs. The designs are either equally supported at placebo $x_1 = \underline{x}$ and a second dose level, say x_2, which depends on the parameters Δ/ϑ_1, ϑ_2, and ϑ_3, or the local MED-optimal designs have weight w_1, w_2, $0.5 - w_1$ and $0.5 - w_2$ at the points $\underline{x}$, x_2, x_3 and $\bar{x}$, respectively, where the points x_2 and x_3 depend on the parameters ϑ_2 and ϑ_3, while the weights w_1 and w_2 depend on the parameters Δ/ϑ_1, ϑ_2, and ϑ_3. These results also indicate the existence of thresholds such that the local MED-optimal designs are supported at two or four points. Some numerical examples are presented in Table 4 for the logistic model. We observe that in most cases the local MED-optimal design for the logistic model requires only two dose levels. Moreover, the efficiency of the standard design is very small. The results for the two beta models show a very similar picture and are depicted in Table 5. It is interesting to note that the performance of the standard design is substantially better for the beta_2 model, which attains its maximum at the dose level $x_{\max} = 100mg$. Here the efficiencies vary between 40% and 56%. The efficiencies for

Table 3: *Local MED-optimal designs for the exponential model (3.10) and the log-linear model (3.11) for various parameters. The dose range is the interval* $[0mg, 150mg]$. *The table also shows the efficiency of the standard design* ξ_s.

Model	Δ	ϑ_1	ϑ_2	x_1	x_2	x_3	w_1	w_2	w_3	eff(ξ_s)
	0.2	0.083	65	0	101.57	150	0.440	0.5	0.060	0.4663
	0.2	0.083	85	0	104.52		0.5	0.5		0.4286
	0.2	0.083	105	0	129.11		0.5	0.5		0.5156
exponential	0.1	0.083	85	0	95.99	150	0.430	0.5	0.070	0.4876
	0.3	0.083	85	0	130.26		0.5	0.5		0.5083
	0.2	0.063	85	0	121.83		0.5	0.5		0.4636
	0.2	0.103	85	0	95.99	150	0.486	0.5	0.014	0.4513
	0.2	0.08	1	0	11.30		0.5	0.5		0.4269
	0.2	0.08	0.6	0	6.78		0.5	0.5		0.3760
	0.2	0.08	1.4	0	15.82		0.5	0.5		0.4550
log-linear	0.1	0.08	1	0	4.05	150	0.468	0.5	0.032	0.4171
	0.3	0.08	1	0	42.13		0.5	0.5		0.5384
	0.2	0.06	1	0	27.51		0.5	0.5		0.5107
	0.2	0.1	1	0	6.43		0.5	0.5		0.3970

the beta$_1$ model with the maximum response attained at the dose level $x_{\max} = 25mg$ are always smaller than 20%.

5 Finite sample properties and robustness

The present section serves several purposes. First, note that the optimality criteria proposed and applied in Sections 3 and 4 for the determination of MED-optimal design are based on asymptotic arguments using a first order expansion for the covariance matrix of the MED estimate. We therefore investigate the finite sample properties of the designs derived from the asymptotic optimality criteria by means of a simulation study. Second, we study the behavior of the optimal designs, if the initial model parameters have been misspecified. Third, we investigate the robustness of the optimal designs if the underlying dose response model has been misspecified.

Table 4: *Local MED-optimal designs for the logistic model for various parameters. The dose range is the interval* $[0mg, 150mg]$*. The table also shows the efficiency of the design* ξ_s*.*

Δ	ϑ_1	ϑ_2	ϑ_3	x_1	x_2	x_3	x_4	w_1	w_2	w_3	w_4	$\text{eff}(\xi_s)$
0.2	0.404	50	7.881	0	49.90			0.5	0.5			0.4124
0.2	0.404	50	10.881	0	50.22			0.5	0.5			0.4094
0.2	0.404	50	13.881	0	51.19			0.5	0.5			0.3998
0.2	0.404	30	10.881	0	32.39			0.5	0.5			0.3202
0.2	0.404	70	10.881	0	69.85			0.5	0.5			0.0879
0.2	0.304	50	10.881	0	57.59			0.5	0.5			0.3116
0.2	0.504	50	10.881	0	45.89			0.5	0.5			0.3064
0.05	0.404	50	10.881	0	37.29	64.44	150	0.401	0.453	0.099	0.047	0.1853
0.1	0.404	50	10.881	0	38.48			0.5	0.5			0.1978
0.3	0.404	50	10.881	0	62.10			0.5	0.5			0.2555

5.1 Finite sample properties

Note that the optimal designs derived in the previous sections are obtained by minimizing the asymptotic variance of the MED estimate for a particular model. For this reason it is important to investigate whether and for which sample sizes the superiority of the optimal designs minimizing the asymptotic variance can be observed in practice. For this purpose we consider as an example the estimate $\widehat{\text{MED}}_2$ for the $E_{\max}$ and the exponential model. The results for the alternative MED estimates and the other models are very similar and, therefore, not included here.
For the dose range $[\underline{x}, \bar{x}] = [0mg, 150mg]$ we simulated data from the model

$$Y = \vartheta_0 + \vartheta_1 f^0(x, \vartheta^0) + \varepsilon$$

where $f^0(x, \vartheta^0) = x/(x + \vartheta_2), \vartheta_0 = 0, \vartheta_1 = 0.466, \vartheta_2 = 25$ for the $E_{\max}$ model and $f^0(x, \vartheta) = \exp(x/\vartheta_2)$, $\vartheta_0 = -0.08265$, $\vartheta_1 = 0.08265$, $\vartheta_3 = 85$ for the exponential model (see Table 1). The clinically relevant effect is $\Delta = 0.2$ and the errors are assumed to be independent and normally distributed with mean 0 and variance $\sigma^2 = 0.01$. Note that in many cases the local MED-optimal designs advise the experimenter to take observations at a smaller number of different dose levels than the number of parameters in the regression model. For this reason there are situations where local MED-optimal designs do not allow the estimation of all parameters in the model (3.1). Moreover, it is possible that a local MED-optimal design for a particular value of ϑ may not allow the estimation of the MED for another value of the parameter, say ρ. In order to address such problems we investigate a slight modification of the local MED-optimal design with $\frac{11 \cdot n}{24}, \frac{n}{2}, \frac{n}{24}$ observations at dose levels $0, 18.75$ and $150mg$ for the $E_{\max}$ model and $\frac{11}{24}n, \frac{n}{2}, \frac{n}{24}$ observations at dose levels $0, 104.5, 150mg$ for the exponential model, respectively. This modification will be

Table 5: *Local MED-optimal designs for the beta$_1$ and the beta$_2$-model, where the parameter $\vartheta_4 = 200$ is fixed. The dose range is the interval $[0mg, 150mg]$. The table also shows the efficiency of the standard design ξ_s.*

model	Δ	ϑ_1	ϑ_2	ϑ_3	x_1	x_2	x_3	x_4	w_1	w_2	w_3	w_4	eff(ξ_s)
	0.2	0.4	0.33	2.31	0	1.26			0.5	0.5			0.120
	0.2	0.4	0.23	2.31	0	0.35			0.5	0.5			0.056
	0.2	0.4	0.43	2.31	0	2.69			0.5	0.5			0.198
beta$_1$	0.2	0.4	0.33	1.71	0	1.66			0.5	0.5			0.167
	0.2	0.4	0.33	2.91	0	1.01			0.5	0.5			0.089
	.05	0.4	0.33	2.31	0	0.49	25.21	106.99	.40	.45	.10	.05	0.140
	0.1	0.4	0.33	2.31	0	0.49	25.20	108.07	.45	.48	.05	.02	0.130
	0.3	0.4	0.33	2.31	0	4.88			0.5	0.5			0.193
	0.2	0.4	1.39	1.39	0	37.34			0.5	0.5			0.399
	0.2	0.4	1.09	1.39	0	26.70			0.5	0.5			0.405
	0.2	0.4	1.69	1.39	0	47.24			0.5	0.5			0.401
beta$_2$	0.2	0.4	1.39	1.09	0	43.26			0.5	0.5			0.398
	0.2	0.4	1.39	1.69	0	32.87			0.5	0.5			0.396
	.05	0.4	1.39	1.39	0	27.00	94.89	150	.39	.45	.11	.05	0.563
	0.1	0.4	1.39	1.39	0	27.00	94.89	150	.45	.48	.05	.02	0.501
	0.3	0.4	1.39	1.39	0	56.76			0.5	0.5			0.420

Table 6: *Simulated standard deviations of the estimate $\widehat{\text{MED}}_2$ for the $E_{\max}$ and the exponential model for the standard design ξ_s and a slight modification $\tilde{\xi}(\vartheta)$ of the local MED-optimal design. The standard deviation is $\sigma = 0.1$.*

	$E_{\max}$				exponential			
n	24	48	96	192	24	48	96	192
ξ_s	10.6	7.5	5.4	3.8	17.1	12.5	9.4	6.7
$\tilde{\xi}(\vartheta)$	8.4	5.6	3.8	2.7	12.4	8.9	6.5	4.5

denoted by $\tilde{\xi}(\vartheta)$ and advises the experimenter to take a small proportion of total observations at the maximum dose level $\bar{x}$ in order to obtain a design, which can be used to estimate all model parameters. In this study we thus compare $\tilde{\xi}(\vartheta)$ with the standard design ξ_s, which places $n/6$

observations at the dose levels $0, 10, 25, 50, 100$, and $150mg$.
In the left part of Table 6 we show the simulated standard deviation of the MED estimate obtained from the two designs for the sample sizes $n = 24$, 48, 96, and 192. The results are based on 300 simulation runs. For both models it follows that the advantages of the local optimal MED-optimal designs derived from the asymptotic theory are also valid for realistic sample sizes. For example, if a clinical team uses 48 patients and allocates the dose levels according to the local MED-optimal design, it obtains the same precision as if it would have used the standard design and 96 patients. The (asymptotic) efficiency defined in (4.3) is also nicely reflected for realistic sample sizes. More precisely, the (asymptotic) efficiency of the standard design ξ_s for the $E_{\max}$ model is 0.46, while the ratio of the finite variances is given by 0.63, 0.56, 0.50, 0.50 for the sample size $n = 24$, 48, 96, 192, respectively. Thus, the conclusions from Section 4 regarding the advantages of local MED-optimal designs obtained from the asymptotic theory hold at least for sample sizes larger than 25.

5.2 Misspecification of the parameters

In this section we study the robustness of local MED-optimal designs with respect to the misspecification of the parameter ϑ. Again, we used the slightly modified local MED-optimal design $\tilde{\xi}(\vartheta)$ described in the previous section, where 4% of the observations are taken at the maximal dose level $\bar{x} = 150mg$, while the remaining 96% patients are treated according to the optimal design. In Table 7 we consider the $E_{\max}$ and the exponential model and display the efficiency

$$\text{eff}(\tilde{\xi}(\vartheta), \rho) = \frac{\Psi(\tilde{\xi}(\vartheta))}{\Psi(\xi^*(\rho))}$$

for various values of ρ, where $\xi^*(\rho)$ is the local MED-optimal design for the specific value ρ under consideration. Here, $\tilde{\xi}(\vartheta)$ is the (modified) local MED-optimal design for the $E_{\max}$ and the exponential model, respectively, where the parameters are chosen as $\vartheta_1 = 0.467, \vartheta_2 = 25$ ($E_{\max}$) and $\vartheta_1 = 0.082625, \vartheta_2 = 85$ (exponential). For example, if the true parameter values are given by $\rho_1 = 0.44$ and $\rho_2 = 15$, the design $\tilde{\xi}(\vartheta)$ calculated under the assumption that the parameters are given by $\vartheta_1 = 0.467, \vartheta_2 = 25$ has an efficiency of 88% for estimating the MED for the $E_{\max}$ model. We observe that the local MED-optimal design $\tilde{\xi}(\vartheta)$ for the exponential model remains very efficient for a broad range of values for ρ_1 and ρ_2. The loss of efficiency caused by a misspecification of the parameters in the $E_{\max}$ model is slightly larger, but the local MED-optimal design $\tilde{\xi}(\vartheta)$ remains reasonably efficient.

5.3 Misspecification of the model

In this section we briefly investigate how local MED-optimal designs derived for a specific model perform if any of the other models considered in Table 1 is the "true" one. We again use the (slightly) modified local MED-optimal designs $\tilde{\xi}(\vartheta)$ described in Section 5.1, where now 4% of the observations are taken at two additional dose levels. The modified designs are displayed in

Table 7: *The efficiency of the design* $\tilde{\xi}(\vartheta) = \{0, 18.75, 150; 0.48, 0.48, 0.04\}$ *for the* $E_{\max}$ *model and the design* $\tilde{\xi}(\vartheta) = \{0, 104.5, 150; 0.48, 0.48, 0.04\}$ *for the exponential model with respect to misspecification of the initial parameters.*

	$E_{\max}$						exponential					
ρ_1	0.432	0.44	7/15	0.48	0.496	0.52	0.0148	0.0442	0.08265	0.126	0.22	0.32
ρ_2	12	15	25	30	36	45	45	65	85	105	145	185
eff	0.72	0.88	0.96	0.91	0.84	0.75	0.74	0.91	0.96	0.95	0.89	0.83

the top part of Table 8, while the corresponding efficiencies for the different models are shown in the bottom part. For example, if the local MED-optimal design $\tilde{\xi}_{[\mathrm{LOG}]}$ (more precisely, its slight modification) for the log-linear model is used for the logistic model, its (asymptotic) variance is 100 times larger than the variance, which could be obtained from the local MED-optimal design $\tilde{\xi}_{[\mathrm{logistic}]}$ for the logistic model. We observe that the local MED-optimal designs are very sensitive with respect to a misspecification of the dose response model. Note that the efficiencies of the standard design ξ_s vary between 40% and 50% for all models except for the beta_1 model. In the following section we will improve the standard design and construct robust and efficient designs with respect to the class of models investigated in this paper.

6 Robust designs with respect to model misspecification

In this section we construct efficient designs for the estimation of the MED, which are robust with respect to the choice of the dose response profile. For this purpose, we assume that there are m candidate models for the dose response curve, say $f_1(x, \vartheta^{(1)}), \ldots, f_m(x, \vartheta^{(m)})$, which are of interest to the experimenter. In the example considered in Section 2 we have $m = 7$ candidate dose response models, see Table 1. We denote by $\xi_j^*(\vartheta^{(j)})$ the local MED-optimal design (for a given value of the unknown parameter $\vartheta^{(j)}$) for the j-th regression model. The efficiency for estimating the MED for the j-th model and a given design ξ is defined as

$$\mathrm{eff}_j(\xi) = \frac{\Psi_j(\xi_j^*(\vartheta^{(j)}))}{\Psi_j(\xi, \vartheta^{(j)})},$$

where Ψ_j is the quantity introduced in (3.7) for the j-th model. The following concept of determining robust designs is a modification of a criterion introduced by Läuter (1974) (see also Pukelsheim and Rosenberger, 1993, Cook and Wong, 1994, Zhu and Wong, 2000, 2001, among many others).

Definition 6.1. *A design is called (local) maximin MED-optimal for the class* $\mathcal{F} = \{f_1, \ldots, f_m\}$ *of candidate dose response models, if it allows the estimation of the MED for all models under consideration and maximizes* $\min\{\mathrm{eff}_j(\xi) \mid j = 1, \ldots, m\}$.

Table 8: *Slightly modified local MED-optimal designs $\tilde{\xi}(\vartheta)$ for the regression models (3.8) - (3.12) (top part) and their efficiencies for the different models (bottom part).*

Model	x_1	x_2	x_3	x_4	w_1	w_2	w_3	w_4
linear	0	50	100	150	0.48	0.02	0.02	0.48
$E_{\max}$	0	18.75	75	150	0.48	0.48	0.02	0.02
exponential	0	104.5	75	150	0.48	0.48	0.02	0.02
log-linear	0	11.3	75	150	0.48	0.48	0.02	0.02
logistic	0	50.2	75	150	0.48	0.48	0.02	0.02
beta_1	0	1.26	75	150	0.48	0.48	0.02	0.02
beta_2	0	37.3	75	150	0.48	0.48	0.02	0.02

Model	$\tilde{\xi}_{[LIN]}$	$\tilde{\xi}_{[E_{\max}]}$	$\tilde{\xi}_{[EXP]}$	$\tilde{\xi}_{[LOG]}$	$\tilde{\xi}_{[logistic]}$	$\tilde{\xi}_{[\text{beta}_1]}$	$\tilde{\xi}_{[\text{beta}_2]}$	ξ_u
linear	0.96	0.10	0.50	0.09	0.17	0.10	0.13	0.50
$E_{\max}$	0.04	0.96	0.01	0.72	0.17	0.05	0.44	0.45
exponential	0.11	0.10	0.97	0.07	0.30	0.06	0.21	0.43
log-linear	0.02	0.62	0.01	0.96	0.06	0.43	0.14	0.43
logistic	0.08	0.02	0.00	0.01	0.96	0.00	0.05	0.41
beta_1	0.00	0.00	0.00	0.01	0.00	0.96	0.00	0.12
beta_2	0.05	0.33	0.01	0.19	0.20	0.01	0.96	0.40

Let $(\alpha_1, \ldots, \alpha_m)$ denote a vector of nonnegative weights with $\sum_{j=1}^m \alpha_j = 1$. A design is called Bayesian MED-optimal for the class $\mathcal{F} = \{f_1, \ldots, f_m\}$ with respect to the prior $(\alpha_1, \ldots, \alpha_m)$, if it allows the estimation of the MED for all models under consideration and maximizes $\sum_{j=1}^m \alpha_j \log \text{eff}_j(\xi)$.

Robust designs in the sense of Definition 6.1 have to be found numerically in all cases of practical interest. We have calculated the optimal designs for the linear, $E_{\max}$, exponential, log-linear, and logistic models considered in Table 1, where a uniform prior is used in the Bayesian criterion. The results are depicted in Table 9, while Table 10 shows the corresponding efficiencies. Note that the maximin criterion leads to a design, which has equal efficiencies for all five models. Moreover, the maximin MED-optimal design has larger efficiencies than the standard design ξ_s for all models under consideration. This is also true for the Bayesian MED-optimal design except for the linear model.

Table 9: *Optimal designs with respect to the maximin and Bayesian optimality criterion (local w.r.t. parameters). The models under consideration are (3.8) -(3.12).*

	x_1	x_2	x_3	x_4	x_5	w_1	w_2	w_3	w_4	w_5
maximin	0	11.2	49.5	115.0	150	0.33	0.19	0.19	0.19	0.11
Bayes	0	9.9	49.5	115.4	150	0.33	0.20	0.23	0.17	0.07

Table 10: *Efficiencies of the optimal designs from Table 9 for the different models (3.8) -(3.12).*

	linear	$E_{\max}$	exponential	log-linear	logistic
maximin	0.53	0.53	0.53	0.53	0.53
Bayes	0.45	0.53	0.52	0.58	0.60

If we extend the model class $\mathcal{F}$ and include the two beta models from Table 1 in the calculation of the robust designs, we observe the maximin and Bayesian optimal designs and their efficiencies in Table 11 and 12, respectively. A comparison of the results from the Tables 10 and 12 shows that the efficiencies are decreasing if the two beta models are included in the robust optimality criteria, which is quite intuitive. The more robustness is required for the design, the less efficient it becomes for the individual dose response model. For example, if we investigate the situation where only concave and increasing dose response models are of interest, the model class $\mathcal{F}$ can be reduced to the linear, $E_{\max}$, log-linear, and logistic models (see Figure 1). The maximin and Bayesian optimal designs are depicted in Table 13. Both criteria lead to designs having approximately 60% efficiency for the four models, while the efficiency of the standard design ξ_s actually being used in the study varies between 40% and 50%.

Table 11: *Optimal designs with respect to the maximin and Bayesian optimality criterion (local w.r.t. parameters). The models under consideration are (3.8) -(3.13).*

	x_1	x_2	x_3	x_4	x_5	x_6	w_1	w_2	w_3	w_4	w_5	w_6
maximin	0	3.4	16.1	49.6	112	150	0.35	0.05	0.14	0.18	0.18	0.10
Bayes	0	2.4	16.7	49.4	104	150	0.35	0.04	0.16	0.20	0.20	0.05

Table 12: *Efficiencies of the optimal designs from Table 11 for the different models (3.8) -(3.13).*

	linear	$E_{\max}$	exponential	log-linear	logistic	beta_1	beta_2
maximin	0.50	0.54	0.55	0.50	0.50	0.50	0.50
Bayes	0.37	0.57	0.58	0.50	0.55	0.53	0.55

Table 13: *Optimal designs with respect to the maximin and Bayesian optimality criterion (local w.r.t. parameters) with their corresponding efficiencies for the different models. The models under consideration are (3.8),(3.9), (3.11), and (3.12).*

	x_1	x_2	x_3	x_4	w_1	w_2	w_3	w_4	linear	$E_{\max}$	log-linear	logistic
maximin	0	11.4	49.4	150	0.33	0.23	0.22	0.22	0.59	0.59	0.59	0.59
Bayes	0	11.2	49.4	150	0.34	0.23	0.24	0.19	0.54	0.60	0.60	0.64

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Appendix A: Proofs

A1: Proof of Theorem 4.1: Note that the function $b(\vartheta)$ defined in (3.6) does not depend on the parameter ϑ_0 and as a consequence the first coordinate of the gradient $b(\vartheta) = \frac{\partial}{\partial\vartheta} a(\vartheta_0, \ldots, \vartheta_p)$ equals 0. Moreover, for the models (3.8) - (3.11) the gradient $b(\vartheta)$ is proportional to a vector of the form $(0, 1, \vartheta_1\gamma(\Delta, \vartheta))^T$, where the function $\gamma(\Delta, \vartheta)$ depends only on Δ/ϑ_1 and ϑ_2. Observing

the definition of the gradient g in (3.4) the statement of Theorem 4.1 is now a consequence of Elfving's theorem (see Elfving, 1952). More precisely, from this result it follows that a design $\xi = \{x_i, w_i\}_{i=1}^k$ is local MED-optimal if and only if there exist numbers $\varepsilon_1, \ldots, \varepsilon_k \in \{-1, 1\}$ such that for some $\lambda \in \mathbb{R}$ the point

$$\lambda\,(0, 1, \vartheta_1\gamma(\Delta, \vartheta))^T = \sum_{j=1}^{k} \varepsilon_j w_j \Big(1, f^0(x_j, \vartheta_2), \vartheta_1 \frac{\partial}{\partial \vartheta_2} f^0(x_j, \vartheta_2)\Big)^T \tag{A .1}$$

is a boundary point of the Elfving set

$$\mathcal{R} = \operatorname{conv}\Big(\Big\{\varepsilon\Big(1, f^0(x, \vartheta), \vartheta_1 \frac{\partial}{\partial \vartheta_2} f^0(x, \vartheta_2)\Big)^T \Big| x \in [\underline{x}, \bar{x}], \varepsilon \in \{-1, 1\}\Big\}\Big), \tag{A .2}$$

where $\operatorname{conv}(A)$ denotes the convex hull of a set $A \subset \mathbb{R}^3$. From the first equation in (A .1) it follows that $k \geq 2$, while the geometry of $\mathcal{R}$ shows $k \leq 3$ and that the placebo $\underline{x}$ must be a support point of the local MED-optimal design (see also Figure 2 where the situation is displayed for the $E_{\max}$ model). If the number of support points equals two, the first equation in (A .1) implies $w_1 = w_2 = 0.5$ (note that in this case $\varepsilon_j = \varepsilon(-1)^j$, $j = 1, 2$ for some $\varepsilon \in \{-1, 1\}$). Similarly, if the MED-optimal design is supported at three points the maximal dose $\bar{x}$ has to be a support point and $\varepsilon_j = (-1)^j\varepsilon$, $(j = 1, 2, 3)$ where $\varepsilon \in \{-1, 1\}$. Now the first equation in (A .1) yields $w_1 - w_2 + w_3 = 0$, which gives in combination with the equation $w_1 + w_2 + w_3 = 1$ the claimed representation for the weights, i.e. $w_2 = 0.5, w_3 = 0.5 - w_1$.

□

A2: Proof of Theorem 4.3 and 4.5: Because all results are proved similarly we restrict ourselves to a proof of Theorem 4.3 (b), which corresponds to the local MED-optimal design problem for the $E_{\max}$ model. For the sake of brevity we use the notation

$$g(x) = (g_1(x), g_2(x), g_3(x))^T = g(x, \vartheta) = \Big(1, f^0(x, \vartheta), \vartheta_1 \frac{\partial}{\partial \vartheta_2} f^0(x, \vartheta)\Big)^T,$$

where $g(x, \vartheta)$ is the gradient defined in (3.4). From Theorem 4.1 it follows that the local MED-optimal design has either two or three support points. Assume first that the local MED-optimal design ξ^* is supported at three points. By Theorem 4.1 we have $x_1 = \underline{x}, x_3 = \bar{x}$ and Elfving's Theorem (see Elfving, 1952) shows that there exists a constant v and a weight w such that the representation

$$-vb(\vartheta) = wg(\underline{x}) - \frac{1}{2}g(x_2) + (w - \frac{1}{2})g(\overline{x})$$

holds and that the point $vb(\vartheta)$ is a boundary point of the corresponding Elfving set defined in (A .2) (see Figure 2). Moreover, the variance in (3.7) of the corresponding design ξ^* is given by $b^T(\vartheta)M^{-1}(\xi^*, \vartheta)b(\vartheta) = 1/v^2$. Putting $b(\vartheta) = (b_1(\vartheta), b_2(\vartheta), b_3(\vartheta))^T$, $w = (1-u)/2$ and considering the second and third coordinate of this system yields the equation

$$\begin{pmatrix} g_2(\overline{x}) - g_2(\underline{x}) & b_2(\vartheta) \\ g_3(\overline{x}) - g_3(\underline{x}) & b_3(\vartheta) \end{pmatrix} \begin{pmatrix} u \\ -2v \end{pmatrix} = \begin{pmatrix} g_2(x_2) - g_2(\underline{x}) \\ g_3(x_2) - g_3(\underline{x}) \end{pmatrix},$$

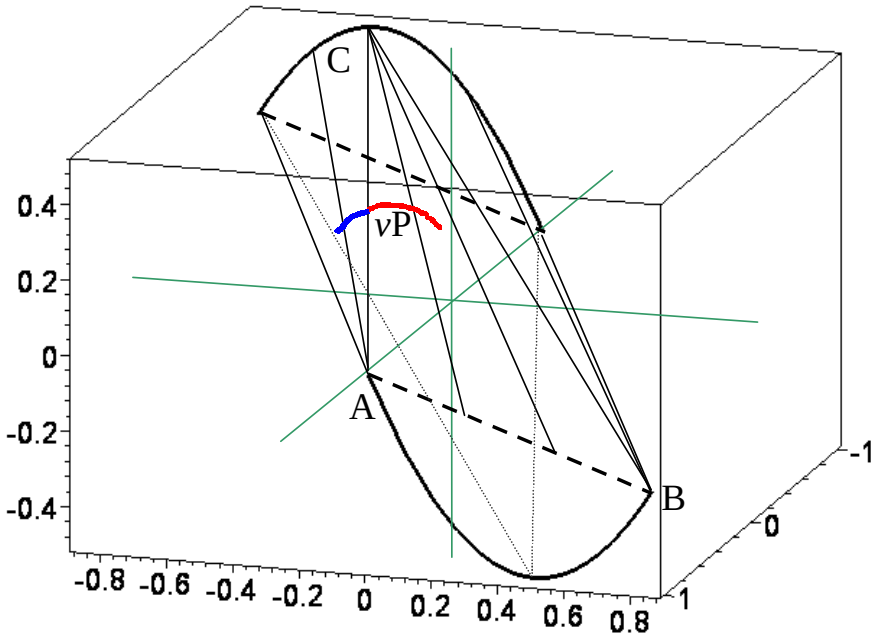

Figure 2: *The Elfving set for the model (3.9) with* $[\underline{x}, \bar{x}] = [0, 3]$, $\vartheta_1 = 1$, $\vartheta_2 = 0.5$. *The points* $g(x_1)$, $-g(x_2)$, *and* $g(x_3)$ *are denoted by* A, B, *and* C, *respectively, while* P *denotes the point* $b(\vartheta)$.

which gives for u and v

$$u = \frac{\begin{vmatrix} g_2(x_2) - g_2(\underline{x}) & b_2(\vartheta) \\ g_3(x_2) - g_3(\underline{x}) & b_3(\vartheta) \end{vmatrix}}{\begin{vmatrix} g_2(\overline{x}) - g_2(\underline{x}) & b_2(\vartheta) \\ g_3(\overline{x}) - g_3(\underline{x}) & b_3(\vartheta) \end{vmatrix}}, \quad -2v = \frac{\begin{vmatrix} g_2(\overline{x}) - g_2(\underline{x}) & g_2(x_2) - g_2(\underline{x}) \\ g_3(\overline{x}) - g_3(\underline{x}) & g_3(x_2) - g_3(\underline{x}) \end{vmatrix}}{\begin{vmatrix} g_2(\overline{x}) - g_2(x_1) & b_2(\vartheta) \\ g_3(\overline{x}) - g_3(\underline{x}) & b_3(\vartheta) \end{vmatrix}}.$$

Maximizing the expression for v with respect to the point x_2 gives the optimal point x_2. For this we determine the point x_2 as a solution of the equation $v' = 0$ and note that this equation can be rewritten as

$$\frac{g_2'(x_2)}{g_3'(x_2)} = \frac{g_2(\overline{x}) - g_2(x_1)}{g_3(\overline{x}) - g_3(\underline{x})}.$$

Solving with respect to x_2 yields the representation (4.1) for the remaining support point of the optimal design, while the weight in (4.2) is obtained from the equation $w = (1 - u)/2$.
From this representation it follows that the local MED-optimal design in the $E_{\max}$ model has three support points if and only if the weight w of the point $x_1 = \underline{x}$ in (4.2) satisfies $w < 0.5$. In particular the weight is a strictly increasing function with respect to the parameter Δ and there exists a point Δ^* such that the local MED-optimal is supported at three points if and only if $\Delta < \Delta^*$. This threshold can be determined considering the weight w in (4.2) as a function of Δ and solving the equation $w(\Delta) = 0.5$, which yields the representation for Δ^*.
Now assume that $w > 0.5$ such that the local MED-optimal design is supported at two points.

In this case we have $x_1 = \underline{x}$ by Theorem 4.1 and Elfving's Theorem yields the representation

$$vb(\vartheta) = \frac{1}{2}g(\underline{x}) - \frac{1}{2}g(x_2),$$

which gives the equations $g_2(x_2) - g_2(\underline{x}) = 2vb_2(\vartheta)$, $g_3(x_2) - g_3(\underline{x}) = 2vb_3(\vartheta)$. Solving with respect to v and x_2 yields the first assertion of Theorem 4.3 (b) for two point designs. □