STATISTICS IN MEDICINE
Statist. Med. 2000; **00**:1–6 *Prepared using* simauth.cls *[Version: 2002/09/18 v1.11]*

Practical considerations for optimal designs in clinical dose finding studies

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SUMMARY

Determining an adequate dose level for a drug and, more broadly, characterizing its dose response relationship, are key objectives in the clinical development of any medicinal drug. If the dose is set too high, safety and tolerability problems are likely to result, while selecting too low a dose makes it difficult to establish adequate efficacy in the confirmatory phase, possibly leading to a failed program. Hence, dose finding studies are of critical importance in drug development and need to be planned carefully. In this paper we focus on practical considerations for establishing efficient study designs to estimate target doses of interest. We consider optimal designs for both the estimation of the minimum effective dose (MED) and the dose achieving $100p\%$ of the maximum treatment effect (ED_p). These designs are compared with D-optimal designs for a given dose response model. Extensions to robust designs accounting for model uncertainty are also discussed. A case study is used to motivate and illustrate the methods from this paper. Copyright © 2000 John Wiley & Sons, Ltd.

KEY WORDS: dose finding, robust designs, model uncertainty, minimum effective dose, dose response, target dose estimation, sample size

1. Introduction

Determining an adequate dose level for a drug and, more broadly, characterizing its dose response relationship, are key objectives in the clinical development process of any medicinal drug. If the dose is set too high, safety and tolerability problems are likely to result, while

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selecting too low a dose makes it difficult to establish adequate efficacy in the confirmatory phase. 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% [1]. 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 results 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. For a recent general discussion of issues and challenges arising in clinical dose finding studies we refer to [2].

An indication of the importance of properly conducted dose response studies is the early publication of the ICH E4 guideline [3], which is the primary source of regulatory guidance in this area. The guideline states in its introductory section that the purpose of dose response information is "*to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effects is seen, but practical study designs do not exist to allow for precise determination of these doses*". Note that the ICH E4 guideline stresses the importance of obtaining good dose response information by estimating relevant target doses. The smallest dose with a discernible useful effect is often characterized as the minimum effective dose (MED), that is, the smallest dose producing a clinically important response that can be declared statistically significantly different from the placebo response [1]. Several methods exist to estimate the MED using either modeling approaches [4, 5] or multiple test strategies [6, 7]. The maximum useful dose, beyond which no further beneficial effects is seen, can similarly be estimated using multiple test strategies [8] or modeling approaches when estimating the smallest dose achieving $100p\%$ of the maximum treatment effect in the observed dose range (ED_p, $0 < p < 1$) [9].

As suggested by the quote above from the ICH E4 guideline, study designs that allow for precise estimation of relevant target doses are hard to derive and, if available, often not applied in clinical practice. In this article we focus on the design of clinical dose finding studies to produce the information needed to efficiently and reliably characterize the benefit of a drug over a dose range of interest. In particular, we consider efficient designs for estimating target doses of interest (i.e, either the MED or an ED_p). Given a fixed number of patients available for the conduct of a clinical dose finding study, we determine 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 asymptotic variance of the target dose estimate is minimized.

In practice, the results in this paper can be used in at least two distinct ways. First, relative efficiencies can be calculated for practically feasible designs. Clinical teams can then balance the additional financial and logistical costs potentially associated with the resulting optimal designs (due to a larger total number of dose levels, the need for producing additional dose levels not considered in the previous studies, etc.) against the benefit of an increased information value resulting from the larger precision in the target dose estimation. The relative efficiencies based on are directly translated into relative sample size requirements and are thus easy to communicate to the clinical teams and decision boards. Second, asymptotic confidence intervals for the target dose can be constructed, which give a quantifiable information on the uncertainty about the target dose estimate estimate under a particular dose response model. In fact, current practice dictates that the sample sizes for clinical dose finding studies are calculated based on power calculations to detect dose response. The resulting sample sizes, however, are often inappropriate for estimating a target dose with a reasonable precision. Prespecifying the width of the confidence interval for the target dose and calculating backwards the necessary sample sizes to achieve the required precision thus puts current practices into a different perspective. Even if the resulting sample sizes of such an approach might not be realistic, the results in this paper can be used to quantify the uncertainty about the target dose estimate, so that the decision makers can balance better the costs and risks based upon the available information.

In the remainder of this paper we formalize the ideas presented in this section and emphasize practical considerations. In Section 2 we describe a case study to put the subsequent discussion into a practical context. In Section 3 we discuss optimal designs to estimate either the MED or an ED_p. These designs are then compared with D-optimal designs, which minimize the volume of the confidence ellipsoid for the dose response model parameters. Finally, we robustify these designs with respect to the underlying true, but unknown dose response model. Practical considerations of these results are discussed when re-visiting the case study in Section 4. Concluding remarks are given in Section 5.

2. A dose finding study for an anti-asthmatic drug

This example refers to a real clinical study in Phase II for the asthma indication. The primary objective of the trial is to select a dose for the Phase III (confirmatory) program. Several active dose levels plus a placebo arm are to be used in the trial, with patients being randomized to one of the treatments (parallel group design). Patients receive one daily dose of their assigned treatment for a total of 14 days. The primary efficacy endpoint of the study is the change from baseline (i.e., the first visit) in the forced expiratory volume measured over one second,

FEV_1, at the end of the study. A placebo effect of 60 mL is assumed with a maximum expected treatment effect increase over placebo of 280 mL and a standard deviation of $\sigma = 350$ mL. The clinically relevant benefit over the placebo effect is set to $\Delta = 200$ mL. That is, an increase in treatment effect of less than 200 mL over the placebo response is considered to be clinically irrelevant.

At the time of designing the study, the clinical team was unsure about the true dose response shape and could in particular not rule out a non-monotonic profile (for example, an umbrella shape). After discussions with the clinical team, several dose response models with associated shapes were identified as plausible to describe the data at study end. The full model specifications of the candidate dose response models are given in Table I and displayed graphically in Figure 1. We refer to [4, 10] for details on the use of candidate models in dose response studies and the elicitation of best guesses for the model parameters.

Model	Full model specification
Linear	$60 + 0.56d$
Beta	$60 + (7/2250)d(600 - d)$
$E_{max\,1}$	$60 + 294d/(25 + d)$
$E_{max\,2}$	$60 + 340d/(107.14 + d)$
Logistic	$49.62 + 290.51/\{1 + \exp[(150 - d)/45.51]\}$

Table I. Candidate dose response models as a function of dose d.

From Figure 1 the uncertainty about the true, but unknown dose response model at the design stage of the study becomes evident. Essentially the entire space of potential dose response shapes is covered by the current selection of candidate models, including two different parameter specifications for the E_{max} model and the inclusion of an umbrella shape (through the Beta model) to cover a potential down-turn in effect at larger doses. The potential impact of the model uncertainty becomes clear, when comparing the associated MED for each of the five candidate model shapes. For illustration purposes, the clinical relevance threshold Δ is included in Figure 1 (horizontal dashed line), together with the resulting MED. For example, for the first E_{max} model the MED is 53.2 μg, whereas the MED is 357.1 μg if the linear model is true. Specifying a single dose response model in the study protocol (with the aim to either determine the experimental design or to specify the final analysis) is thus not possible given the uncertainty about the true model and the potential impact on the study outcome.

Given the information and constraints described above, the clinical team was then faced with the decision of how many dose levels k to include in the study, which dose levels $d_1, \ldots, d_k$ to investigate, whether to use an unbalanced allocation of the patients to the dose levels d_i, and how to determine the total sample size n. In the following section we discuss methods to

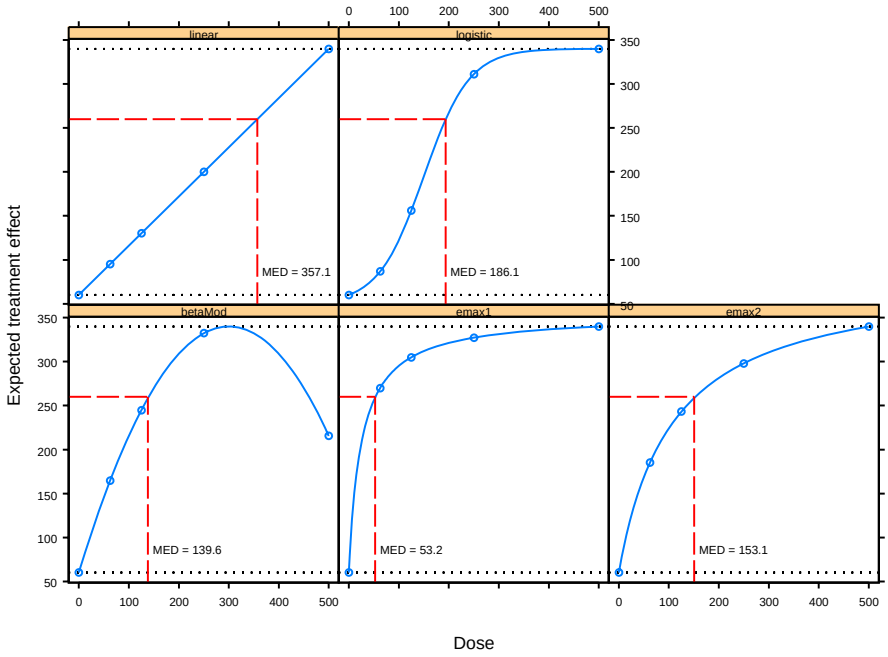

Figure 1. Dose response models corresponding to the models in Table I. Open dots indicate the four active dose levels – 62.5, 125, 250, and 500 μg – plus a placebo arm finally used in the clinical study.

address these questions and apply the results when re-visiting the case study in Section 4.

3. Efficient designs for target dose estimation

In this section we consider optimal designs for both the estimation of the MED and the ED_p. These designs are compared with D-optimal designs for a given dose response model. We use the $\mathrm{E}_{\max}$ to illustrate the various designs, although the results can be extended to other common dose response models, such as those shown in Table I. Extensions to robust designs accounting for model uncertainty are also discussed.

3.1. Notation

We consider the non-linear regression model

$$Y_{ij} = f(d_i, \vartheta) + \varepsilon_{ij}, \tag{1}$$

where Y_{ij} denotes the response of patient j at dose $d_i, i = 1, \ldots, k$, $j = 1, \ldots, n_i$, $f(.)$ denotes the true, but unknown dose response model determined through the parameter vector $\vartheta = (\vartheta_0, \vartheta_1, \vartheta^0)^T = (\vartheta_0, \vartheta_1, \ldots, \vartheta_\ell)^T \in \mathbb{R}^{\ell+1}$, and ε_{ij} denote the residual errors, which are assumed to be independent normal distributed with common variance σ^2. Example model specifications for the function $f(d, \vartheta)$ are given in Table I.

As mentioned in the Introduction, we consider in this article two different target doses, the MED and the ED_p, which are introduced formally now. Let $\underline{d}$ ($\overline{d}$) denote the lowest (highest) dose within the dose range $[\underline{d}, \overline{d}]$ under investigation, where often $\underline{d} = 0$ is the placebo dose. For a given clinically relevant effect Δ, the MED associated with a model $f(d, \vartheta)$ is defined as

$$\mathrm{MED} = \inf\{d \in (\underline{d}, \overline{d}] : f(d, \vartheta) \geq f(\underline{d}, \vartheta) + \Delta\}.$$

Note that the MED does not need to exist, as no dose in $(\underline{d}, \overline{d}]$ may produce an improvement of Δ over $f(\underline{d}, \vartheta)$. We restrict the MED to lie within the interval $(\underline{d}, \overline{d}]$ in order to avoid problems arising from extrapolating beyond the dose range under investigation. Following [10], we use

$$\widehat{\mathrm{MED}} = \inf\{d \in (\underline{d}, \overline{d}] : f(d, \hat{\vartheta}) \geq f(\underline{d}, \hat{\vartheta}) + \Delta, L_d > f(\underline{d}, \hat{\vartheta})\}$$

to estimate the MED, where L_d denotes the lower $1 - \gamma$ confidence bound for the expected value $f(d, \hat{\vartheta})$ at dose d and $\hat{\vartheta}$ denotes the non-linear least squares estimate of ϑ.

Let $h(d, \vartheta) = f(d, \vartheta) - f(\underline{d}, \vartheta)$ denote the effect difference at the doses $d \in (\underline{d}, \overline{d}]$ and $\underline{d}$. Following [2], the ED_p can then be defined as

$$\mathrm{ED}_p = \inf\left\{d \in (\underline{d}, \overline{d}] : \frac{h(d, \vartheta)}{h(d_{\max}, \vartheta)} \geq p\right\},$$

where $d_{\max} = \mathrm{argmax}_{d \in (\underline{d}, \overline{d}]} h(d, \vartheta)$ denotes the dose corresponding to the maximum effect difference in the interval $(\underline{d}, \overline{d}]$. Unlike the MED, the ED_p always exists. If L'_d denotes the lower $1 - \gamma$ confidence bound for the expected value $h(d, \vartheta)$ at dose d, we can estimate ED_p by

$$\widehat{\mathrm{ED}_p} = \inf\left\{d \in (\underline{d}, \overline{d}] : \frac{h(d, \hat{\vartheta})}{h(\hat{d}_{\max}, \hat{\vartheta})} \geq p, L'_d > 0\right\},$$

where $\hat{d}_{\max} = \mathrm{argmax}_{d \in (\underline{d}, \overline{d}]} h(d, \hat{\vartheta})$.

Finally, let

$$\xi = \begin{pmatrix} d_1 & \ldots & d_k \\ w_1 & \ldots & w_k \end{pmatrix}$$

denote an experimental design with relative allocation w_i of patients at doses $d_i, i = 1, \ldots, k$. Following [11], the weights $w_i \geq 0$, with $\sum_{i=1}^k w_i = 1$, are not necessarily multiples of $1/n$, where n denotes the total sample size. In practice, for a given sample size n, a design ξ is implemented by rounding the quantities $w_i n$ to integers, say n_i, with $\sum_{i=1}^k n_i =$

n (approximate design theory). We denote by $M(\xi,\vartheta) = \sum_{i=1}^{k} w_i g(d_i,\vartheta) g^T(d_i,\vartheta)$ the information matrix of the design ξ in the regression model (1), where

$$g^T(d,\vartheta) = \frac{\partial f(d,\vartheta)}{\partial \vartheta} = \Big(1, f^0(d,\vartheta^0), \vartheta_1 \frac{\partial f^0(d,\vartheta^0)}{\partial \vartheta_2}, \ldots, \vartheta_1 \frac{\partial f^0(d,\vartheta^0)}{\partial \vartheta_\ell}\Big) \in \mathbb{R}^{\ell+1}$$

denotes the gradient of the response function f with respect to the parameter vector ϑ. The matrix $M(\xi,\vartheta)$ can be interpreted as a measure of precision of the parameter estimate $\hat{\vartheta}$ based on the design ξ. "Larger" values of $M(\xi,\vartheta)$ indicate better (i.e., more precise) estimates of $\hat{\vartheta}$.

3.2. Optimal designs for MED estimation

Using Elfving's theorem [12], Dette et al. [13] investigated optimal designs to estimate the MED for several practical relevant dose response models. They derived general results, but omitted some of the explicit expressions for the individual models. In the following we derive the necessary expressions for the situations considered in the present paper. To keep the discussion concrete, we focus on the $\mathrm{E}_{\max}$ model

$$f(d,\vartheta) = \vartheta_0 + \vartheta_1 \frac{d}{\vartheta_2 + d} \tag{2}$$

to illustrate the concepts. In the $\mathrm{E}_{\max}$ model (2), ϑ_0 denotes the placebo effect at dose $d = 0$, ϑ_1 denotes the asymptotic maximum treatment effect achieved at an infinite dose, and ϑ_2 denotes the ED_{50}, i.e., the dose that gives 50% of the maximum treatment effect [4, 14]. The motivation to focus on the $\mathrm{E}_{\max}$ model is its ubiquitous use in clinical practice. In particular, the $\mathrm{E}_{\max}$ can be justified on the relationship of drug-receptor interactions and therefore deduced from the chemical equilibrium equation [15].

We consider first the gradient

$$g(d,\vartheta) = \Big(1, \frac{d}{d+\vartheta_2}, \frac{-\vartheta_1 d}{(d+\vartheta_2)^2}\Big)^T$$

of $f(d,\vartheta)$ with respect to ϑ for the $\mathrm{E}_{\max}$ model (2). Figure 2 plots the partial derivatives as a function of the dose d for the two $\mathrm{E}_{\max}$ models specified in Table I. The $\mathrm{E}_{\max 1}$ model, which has the smaller ϑ_2 ($= \mathrm{ED}_{50}$) value and the steeper increase to the plateau level, has considerably larger values for the first derivatives at smaller doses than the $\mathrm{E}_{\max 2}$ model. This will be reflected when calculating optimal designs, which account for the dose ranges with the potential largest amount of information.

The variance of the MED-estimate $\widehat{\mathrm{MED}}$ for a general dose response model f is given by $\sigma^2 \Psi_{\mathrm{MED}}(\xi)/n$, where $\Psi_{\mathrm{MED}}(\xi) = b^T(\vartheta_0,\ldots,\vartheta_\ell) M^-(\xi,\vartheta) b(\vartheta_0,\ldots,\vartheta_\ell)$ and the vector b denotes the gradient of the function $f^{-1}\big(\frac{\Delta}{\vartheta_1} + f(\underline{d},\vartheta)\big)$ with respect to ϑ [13]. For the $\mathrm{E}_{\max}$ model (2)

$$b(\vartheta_0,\vartheta_1,\vartheta_2) = -\frac{r(\vartheta_2+\underline{d})}{(r\underline{d} - \vartheta_2(r-1))^2} \left(0, \frac{\vartheta_2}{\vartheta_1}(\underline{d}+\vartheta_2), (r-1)\vartheta_2 + \underline{d}(1+r)\right)^T,$$

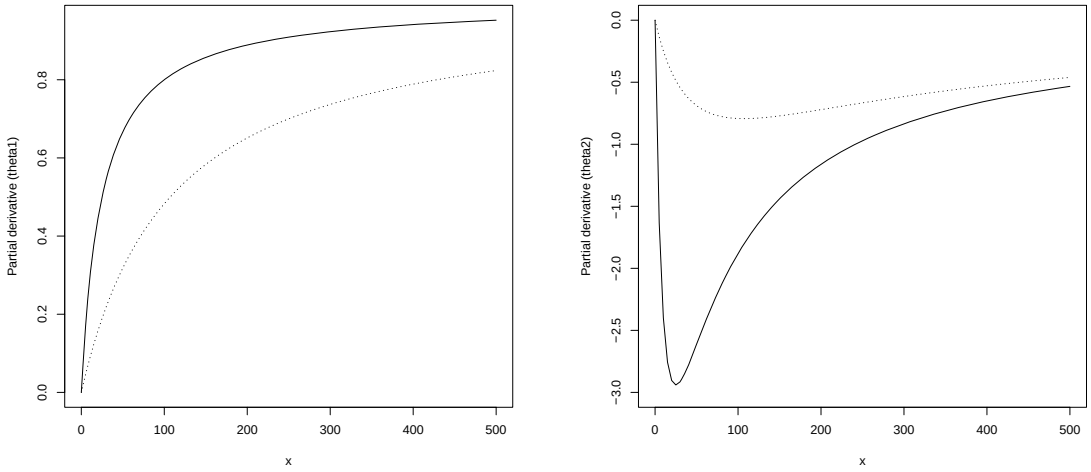

Figure 2. Partial derivatives for the two $\mathrm{E}_{\max}$ models specified in Table I. Left plot: $d/(d+\vartheta_2)$; right plot: $-\vartheta_1 d/(d+\vartheta_2)^2$. Solid line: $\mathrm{E}_{\max 1}$ model; dotted line: $\mathrm{E}_{\max 2}$ model

where $r = \Delta/\vartheta_1$. A design ξ^*_{MED} is called MED-optimal if it minimizes $\Psi_{\mathrm{MED}}(\xi)$ among all designs ξ for which the MED is estimable. Such optimal designs can be calculated explicitly for common dose response models with $\ell + 1 = 2$ or 3 model parameters; otherwise, numerical optimization methods have to be used [13]. For the $\mathrm{E}_{\max}$ model (2), for example, the optimal design ξ^*_{MED} is either a two point design or a three point design, depending on – loosely speaking - the relative position of the MED: If the $\mathrm{E}_{\max}$ model increases steeply at smaller doses and the threshold Δ is small, two points are not sufficient to guarantee a precise MED estimate. It is noteworthy that if a two-point design is optimal for the $\mathrm{E}_{\max}$ model, the non-trivial support point matches exactly the expected MED. Consequently, the optimal designs for the two $\mathrm{E}_{\max}$ models specified in Table I are given by

$$\xi^*_{\mathrm{MED}}(\mathrm{E}_{\max 1}) = \begin{pmatrix} 0 & 53.19 \\ 0.5 & 0.5 \end{pmatrix} \quad \text{and} \quad \xi^*_{\mathrm{MED}}(\mathrm{E}_{\max 2}) = \begin{pmatrix} 0 & 153.06 \\ 0.5 & 0.5 \end{pmatrix}.$$

Note that the second support point d_2 is considerably smaller for the $\mathrm{E}_{\max 1}$ model than for the $\mathrm{E}_{\max 2}$ model, which is also consistent with Figure 2. In practice, a two-point design will not be sufficient to estimate an $\mathrm{E}_{\max}$ model, which has $\ell = 3$ parameters and thus requires at least three support points. In such situations we recommend to use a slight modification of the optimal design by allocating a small fraction of patients to an additional dose. In the previous

example, one could use

$$\tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 1}) = \begin{pmatrix} 0 & 53.19 & 500 \\ 0.45 & 0.45 & 0.1 \end{pmatrix} \quad \text{and} \quad \tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 2}) = \begin{pmatrix} 0 & 153.06 & 500 \\ 0.45 & 0.45 & 0.1 \end{pmatrix}$$

instead of $\xi^*_{\mathrm{MED}}(\mathrm{E}_{\max 1})$ and $\xi^*_{\mathrm{MED}}(\mathrm{E}_{\max 2})$, respectively.

Extending the results from [13], one can derive analytical expressions for the variance of the MED-estimate under an optimal design ξ^*_{MED}. For the $\mathrm{E}_{\max}$ model one obtains

$$\Psi_{\mathrm{MED}}\big(\xi^*_{\mathrm{MED}}\big) = \frac{4\vartheta_2^2(d_1+\vartheta_2)^4}{\vartheta_1^2(\vartheta_2 - r(d_1+\vartheta_2))^4}$$

if the optimal design is a two-point design and

$$\Psi_{\mathrm{MED}}\big(\xi^*_{\mathrm{MED}}\big) = \frac{8^2 r^2 (d_1+\vartheta_2)^6 (d_3+\vartheta_2)^2 ((d_1-d_3)\vartheta_2 + (d_1+d_3)r\vartheta_2 + (d_1 d_3 + \vartheta_2^2)r)^2}{\vartheta_2^2\vartheta_1^2(d_3-d_1)^4(rd_1+(r-1)\vartheta_2)^2}$$

if the optimal design is a three point design. Applying these formulas to our numerical example from Table I, this gives $\Psi_{\mathrm{MED}}\big(\xi^*_{\mathrm{MED}}\big) = 2.77$ for the $\mathrm{E}_{\max 1}$ model and $\Psi_{\mathrm{MED}}\big(\xi^*_{\mathrm{MED}}\big) = 13.82$ for the $\mathrm{E}_{\max 2}$ model.

In fact, we can not only establish the expected variance of the MED estimate using the expressions above, but also calculate an (asymptotic) confidence interval for the MED. Relying on the large sample normal approximation, we have

$$\left[\widehat{\mathrm{MED}} - z_{1-\frac{\alpha}{2}}\hat{\sigma}\sqrt{\frac{\Psi_{\mathrm{MED}}(\xi)}{n}};\ \widehat{\mathrm{MED}} + z_{1-\frac{\alpha}{2}}\hat{\sigma}\sqrt{\frac{\Psi_{\mathrm{MED}}(\xi)}{n}}\right], \tag{3}$$

where $z_{1-\alpha/2}$ denotes the $1-\alpha/2$ quantile of the standard normal distribution. Optimal designs ξ^*_{MED}, which minimize $\Psi_{\mathrm{MED}}(\xi)$, consequently minimize the expected width of the confidence interval for the MED. If we plug in the expected standard deviation of $\sigma = 350$ from Section 2, set $\alpha = 0.05$ and assume a total of $n = 100$ patients, we obtain the expected confidence intervals $[-60.92; 167.32]$ for the $\mathrm{E}_{\max 1}$ model and $[-101.89; 408.09]$ for the $\mathrm{E}_{\max 2}$ model. As expected from the previous discussions, the $\mathrm{E}_{\max 1}$ model provides a more precise estimate of the MED estimate than the the $\mathrm{E}_{\max 2}$ model, since it is considerably steeper around the expected MED. Note, however, the large width of the expected confidence interval, which in case of the $\mathrm{E}_{\max 2}$ model covers almost the entire dose range under investigation if only 100 patients were used in total. In Section 4 we discuss how to calculate the necessary sample size for a dose finding study to meet a pre-specified precision of the MED estimate based on the expected width of the confidence interval in (3).

3.3. Optimal designs for ED_p estimation

We now consider optimal designs to estimate the ED_p for a given $0 < p < 1$. Similar as for the MED estimation problem, the variance of the ED_p-estimate $\widehat{\mathrm{ED}_p}$ for a general dose response

model f is given by $\sigma^2\Psi_{\mathrm{ED_p}}(\xi)/n$, where $\Psi_{\mathrm{ED_p}}(\xi) = c^T(\vartheta_0,\ldots,\vartheta_p)M^-(\xi,\vartheta)c(\vartheta_0,\ldots,\vartheta_p)$, $M(\xi,\vartheta)$ is as defined in Section 3.1, and the vector c denotes the gradient of the function $f^{-1}(f(\underline{d},\vartheta)+p(f(d_{\max},\vartheta)-f(\underline{d},\vartheta)))$ with respect to ϑ. A design $\xi^*_{\mathrm{ED}_p}$ is called ED_p-optimal if it minimizes $\Psi_{\mathrm{ED_p}}(\xi)$ among all designs ξ. Using Elfving's theorem [12], such optimal designs can be calculated analytically for common dose response models with $\ell+1=2$ or 3 model parameters; otherwise, numerical optimization methods have to be used. It can be shown that the vector $c(\vartheta)$ does not depend neither on ϑ_0 nor on ϑ_1 and consequently is of the form $c(\vartheta)=\gamma(0,0,c_1,\ldots,c_{\ell-1})^T$ for a same constant γ. For example, in the $\mathrm{E_{max}}$ model we have

$$c(\vartheta) = \frac{p(1-p)(\overline{d}-\underline{d})^2}{(\vartheta_2+p\underline{d}+(1-p)\overline{d})^2}(0,0,1)^T.$$

This implies that for dose response models with $\ell+1=3$ parameters the ED_p-optimal designs do not depend on p.

As for the MED estimation problem, we use the $\mathrm{E_{max}}$ model (2) to illustrate the explicit expressions. The optimal design $\xi^*_{\mathrm{ED}_p}$ for the $\mathrm{E_{max}}$ model is given by

$$\xi^*_{\mathrm{ED}_p} = \begin{pmatrix} d_1 & d(\vartheta) & d_3 \\ 0.25 & 0.5 & 0.25 \end{pmatrix},$$

where the dose level $d(\vartheta)$ is defined by

$$d(\vartheta) = \frac{\vartheta_2\underline{d}+\vartheta_2\overline{d}+2\overline{d}\underline{d}}{2\vartheta_2+\underline{d}+\overline{d}}. \tag{4}$$

It is noteworthy that the ED_p-optimal design (4) does not depend on the particular value p and that the support points coincide with those of the MED-optimal design in the case where this optimal design has three dose levels. Applying (4), the optimal designs for the two $\mathrm{E_{max}}$ models specified in Table I are given by

$$\xi^*_{\mathrm{ED}_p}(\mathrm{E_{max\,1}}) = \begin{pmatrix} 0 & 22.727 & 500 \\ 0.25 & 0.5 & 0.25 \end{pmatrix} \quad \text{and} \quad \xi^*_{\mathrm{ED}_p}(\mathrm{E_{max\,2}}) = \begin{pmatrix} 0 & 74.999 & 500 \\ 0.25 & 0.5 & 0.25 \end{pmatrix}$$

for any $0<p<1$. Note that the second support point d_2 is considerably smaller for the $\mathrm{E_{max\,1}}$ model than for the $\mathrm{E_{max\,2}}$ model, which is consistent with the previous findings for the MED estimation problem. Although the ED_p-optimal design does not depend on the specific value of p, this quantity enters in the asymptotic variance of the ED_p-estimate $\widehat{\mathrm{ED}_p}$ under the ED_p-optimal design $\xi^*_{\mathrm{ED}_p}$, which is given by

$$\Psi_{\mathrm{ED}_p}\big(\xi^*_{\mathrm{ED}_p}\big) = \left(\frac{8p(1-p)(\vartheta_2+d_1)^2(\vartheta_2+d_3)^2}{\vartheta_1\vartheta_2(\vartheta_2+pd_1+(1-p)d_3)^2}\right)^2.$$

Figure 3 plots $\Psi_{\mathrm{ED}_p}\big(\xi^*_{\mathrm{ED}_p}\big)$ as a function of p for the two $\mathrm{E_{max}}$ models specified in Table I. The $\mathrm{E_{max\,1}}$ model, which has the smaller ϑ_2 ($=\mathrm{ED}_{50}$) value and the steeper increase to the

plateau level, leads to considerably smaller variances of $\widehat{\mathrm{ED}_p}$ than the $\mathrm{E}_{\max 2}$ model for most $p \in (0,1)$. Recall from Section 3.2 the values $\Psi_{\mathrm{MED}}\left(\xi^*_{\mathrm{MED}}\right) = 2.77$ for the $\mathrm{E}_{\max 1}$ model and $\Psi_{\mathrm{MED}}\left(\xi^*_{\mathrm{MED}}\right) = 13.82$ for the $\mathrm{E}_{\max 2}$ model. Thus, the MED is estimated with larger variance under the MED-optimal design than the ED_p under the ED_p-optimal design for the $\mathrm{E}_{\max 2}$ model for all $p \in (0,1)$. The same is also true the $\mathrm{E}_{\max 1}$ model for $p < 0.75$. Note that the maximum value of $\Psi_{\mathrm{ED}_p}\left(\xi^*_{\mathrm{ED}_p}\right)$ is numerically the same for both $\mathrm{E}_{\max}$ models in Figure 3. Finally we note that asymptotic confidence intervals for the ED_p can be constructed similarly to equation (3) for the MED.

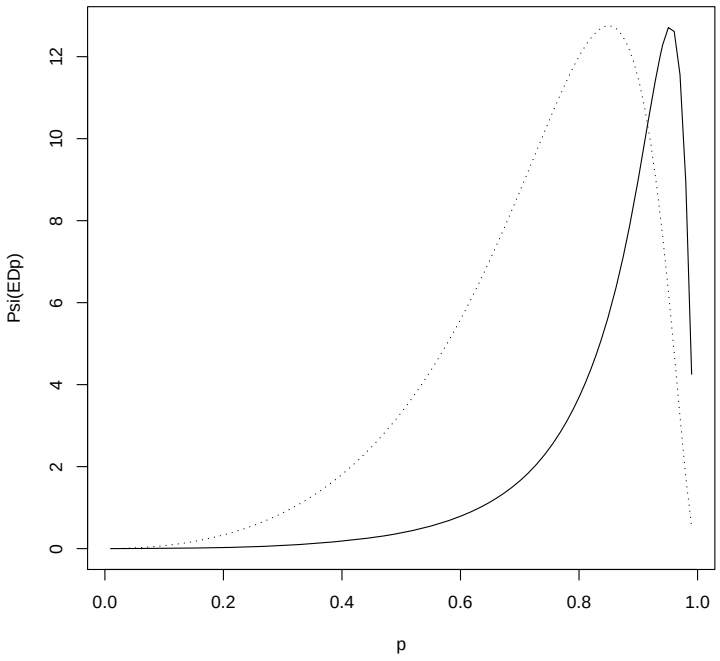

Figure 3. The function $\Psi_{\mathrm{ED}_p}\left(\xi^*_{\mathrm{ED}_p}\right)$ for the two $\mathrm{E}_{\max}$ models specified in Table I. Solid line: $\mathrm{E}_{\max 1}$ model; dotted line: $\mathrm{E}_{\max 2}$ model. The asymptotic variance of $\widehat{\mathrm{ED}_p}$ under the ED_p-optimal design $\xi^*_{\mathrm{ED}_p}$ is given by $\sigma^2 \Psi_{\mathrm{ED}_p}\left(\xi^*_{\mathrm{ED}_p}\right)/n$

3.4. D-optimal designs for dose response estimation

In the previous sections we used c-optimal designs to minimize the variance of a target dose estimate (either the MED or an ED_p). Often it is argued that the optimal designs for one target

dose might be very inefficient for another target dose. Instead, D-optimal designs are proposed in the context of dose response studies, which focus on minimizing simultaneously the variance for all model parameter estimates [16, 17]. D-optimal designs operate on the determinant of the information matrix $M(\xi, \vartheta)$ and minimize the volume of the confidence ellipsoid for the dose response model parameters, thus focusing on the entire dose response relationship instead of a single dose.

Closed form expressions can often be derived by standard arguments using the equivalence theorem for the D-optimality criteria [18]. For example, it can be shown that for the $\mathrm{E}_{\max}$ model the D-optimal design has equal weights at three points, which coincide with the support points of the ED_p-optimal design [19]. Similar results hold also for the other models in Table I with $\ell \leq 3$ parameters. This indicates that for these models the D-optimal designs are rather efficient to estimate the ED_p and vice versa. It follows from [19] that the D-optimal design ξ^*_{D} for the $\mathrm{E}_{\max}$ model (2) is given by

$$\xi^*_{\mathrm{D}} = \begin{pmatrix} d_1 & d(\vartheta) & d_3 \\ 0.\overline{3} & 0.\overline{3} & 0.\overline{3} \end{pmatrix},$$

where the dose level $d(\vartheta)$ is defined in (4). Consequently, the D-optimal designs for the two $\mathrm{E}_{\max}$ models specified in Table I are given by

$$\xi^*_{\mathrm{D}}(\mathrm{E}_{\max 1}) = \begin{pmatrix} 0 & 22.727 & 500 \\ 0.\overline{3} & 0.\overline{3} & 0.\overline{3} \end{pmatrix} \quad \text{and} \quad \xi^*_{\mathrm{D}}(\mathrm{E}_{\max 2}) = \begin{pmatrix} 0 & 74.999 & 500 \\ 0.\overline{3} & 0.\overline{3} & 0.\overline{3} \end{pmatrix}.$$

As mentioned above, the support points of the ED_p- and D-optimal designs coincide, and it would be of interest to investigate the relative efficiencies between these two and the MED-optimal design. Relative efficiencies are proportional to the sample size needed for a given design ξ to achieve the same precision for parameter estimation as a reference designs, e.g., an optimal design ξ^* in our case. If, for example, the relative efficiency of ξ versus ξ^* is 0.5, then the optimal design ξ^* would need only half of the patients to achieve the same precision (e.g., for the MED or ED_p estimation) as a given design ξ. Consequently, in case of MED or ED_p estimation, the optimal design ξ^* would lead to 30% shorter confidence intervals than a given design ξ. For our purposes, the relative efficiencies are defined by

$$\begin{aligned} \mathrm{eff}_{\mathrm{D}}(\xi) &= \left(\frac{|\, M(\xi, \vartheta)\,|}{|\, M(\xi^*_{\mathrm{D}}, \vartheta)\,|} \right)^{1/3}, \\ \mathrm{eff}_{\mathrm{ED}_p}(\xi) &= \frac{\Psi^*_{\mathrm{ED}_p}(\xi_{\mathrm{ED}_p})}{\Psi_{\mathrm{ED}_p}(\xi)}, \\ \mathrm{eff}_{\mathrm{MED}}(\xi) &= \frac{\Psi^*_{\mathrm{MED}}(\xi_{\mathrm{MED}})}{\Psi_{\mathrm{MED}}(\xi)}. \end{aligned}$$

In Table II we use the $\mathrm{E}_{\max 1}$ model to show the efficiencies of the different designs for the different estimation problems; the efficiencies for the $\mathrm{E}_{\max 2}$ model are similar and therefore

omitted. Note that the MED-optimal design is supported at only two points and does not allow the estimation of all model parameters. We therefore use the slightly modified $\tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 1})$ from Section 3.2, which allocates 10% of the patients to the highest dose. We observe reasonable D- and ED_p-efficiencies for the ED_p- and D-optimal design, respectively. The MED-efficiencies for these designs are 66% and 73%. On the other hand, the MED-optimal design has a rather poor performance to estimate the ED_p.

Design	Relative efficiency		
	$\mathrm{eff}_{\mathrm{D}}(\xi)$	$\mathrm{eff}_{\mathrm{ED}_p}(\xi)$	$\mathrm{eff}_{\mathrm{MED}}(\xi)$
ξ^*_D	1	0.8889	0.7334
$\xi^*_{\mathrm{ED}_p}$	0.9449	1	0.6587
$\tilde{\xi}^*_{\mathrm{MED}}$	0.7142	0.3551	0.9401

Table II. *Relative efficiencies of D-, ED_p- and MED-optimal designs for the $E_{\max 1}$ model.*

3.5. Robust designs

All the designs considered so far are locally optimal in the sense that they are constructed for a particular dose response shape. That is, the optimality of a design ξ^* holds for the dose response model f and associated parameter vector ϑ, for which it is constructed. Dette et al. [13] investigated the robustness of MED-optimal designs with respect to their assumptions. Their results suggests that locally optimal designs are moderately robust with respect to a misspecification of the model parameters, but highly sensitive with respect to a misspecification of the regression function.

In practice, we recommend for any type of estimation problem the use of model robust designs introduced below, which are less sensitive with respect to the choice of the regression model. The following considerations are generic and hold for robustifying either MED-, ED_p-, or D-optimal designs considered in the previous sections. The key idea is to assume m regression models $f_1(d, \vartheta^{(1)}), \ldots, f_m(d, \vartheta^{(m)})$, calculate optimal designs for each of these models using the methods above and finally aggregate the information to construct a robust design. In the following we apply two generic approaches from the literature [20, 21, 22] to the estimation problems considered here. The relative performance of both types of robust design will be illustrated when re-visiting the case study in Section 4. Since the results are generic, we drop in the following the subscripts indicating whether MED-, ED_p-, or D-robust designs are considered.

We first consider maximin designs, which maximize the minimum efficiency of a given design relative to the optimal designs for the m regression models under investigation. That is, given the m regression functions $f_j(d, \vartheta^{(j)})$ with associated optimal designs ξ^*_j, $j = 1, \ldots, m$, a

design is called maximin optimal if it maximizes $\min\{\text{eff}_1(\xi), \ldots, \text{eff}_m(\xi)\}$ among all designs ξ, where $\text{eff}_j(\xi)$ denotes the efficiency of a design ξ in the jth model ($j = 1, \ldots, m$) with respect to the optimal design for the model under consideration. The maximin design can therefore be thought of as safeguarding against the worst case scenario, since the minimum relative efficiency is maximized. An alternative approach is to assign probabilities $\alpha_1, \ldots, \alpha_m$ with $\sum_{j=1}^m \alpha_j = 1$ to each of the m regression models and subsequently to maximize the weighted sum $\sum_{j=1}^m \alpha_j \log \text{eff}_j(\xi)$, leading to so-called Bayesian optimal designs. The model probabilities may reflect the clinical team believes about the importance or likelihood for a particular model. If no prior information is available and all models are equally relevant, a reasonable choice is to use equal weights $\alpha_1 = \ldots = \alpha_m = 1/m$. Note that response-adaptive designs could be used, where data of an ongoing clinical study is used to update the prior information about the weights α_j in order to calculate a Bayesian optimal design for subsequent cohorts of patients. Such flexibility is not available for maximin designs.

4. Application to case study

We now revisit the case study from Section 2 to apply some of the results from the previous section. For simplicity, we keep the discussion focused on estimating the MED, since the considerations below apply equally to other problems, including the results for ED_p- and D-optimal designs from Section 3.

Recall from Section 2 that the main open questions at the design stage of the study under investigation are the number k of dose levels, the choice of the dose levels $d_1, \ldots, d_k$, whether to use an unbalanced allocation of the patients to the dose levels d_i or not, and the total sample size n. Given the inherent model uncertainty problem, we calculate both maximin and Bayes designs based on the $m = 5$ dose response models specified in Table I. Since no model is assumed to be more likely than others, equal prior weights $\alpha_i = 1/5$ are assigned to each of the models. Note that in practice the choice of the dose levels to be investigated in a clinical study is often restricted by manufacturing or other constraints. That is, not all doses from the continuous interval $[\underline{d}, \overline{d}]$ can be investigated in a clinical study. In the current study, such logistical considerations let the clinical team to randomize the patients to the four active dose levels 62.5, 125, 250, and 500 μg plus a placebo (denoted in the following as *actual* dose levels; they are indicated by the open dots in Figure 1). Since restricting the space of admissible doses has an impact on the choice of the final design and its efficiency, we consider below both the unrestricted and the restricted case. To be more specific, we consider maximin and Bayesian optimal designs for the following scenarios:

(A) Unrestricted search for a robust design over the continuous interval $[\underline{d}, \overline{d}] = [0, 500]$
(B) Restricted search for a robust design given the actual dose levels 0, 62.5, 125, 250, and

500 μg

(C) Restricted search for a robust design given the dose levels from (A)

Note that for scenarios (B) and (C) the design search is restricted in determining the allocation ratios w_i for the given doses.

Table III provides the results from the calculations for the total of six different cases. Consider first the maximin designs in the upper half of Table III. Allowing for an unrestricted design search in $[\underline{d}, \overline{d}]$ in scenario (A), the maximin design is a five-point design, which allocates roughly 36%, 20%, 22%, 6% and 16% of the patients to the dose levels 0, 49, 177, 452 and 500 μg, respectively. The efficiency of the maximin design relative to the optimal designs for each of the models under consideration is given in the right column of Table III. If we restrict the design search to the actual dose levels, we obtain the results given under scenario (B). Note that the relative efficiencies of the design under scenario (B) are uniformly better than those under scenario (A). This might look counterintuitive at first sight, since under scenario (B) we are restricting the design space considerably by specifying the five dose levels. One might assume that such restriction would lead to inferior designs as compared to scenario (A). Note, however, that the maximin designs depend on the individual optimal designs, which are different under (A) and (B). More precisely, the efficiencies under scenario (A) are calculated with respect to the optimal designs for the individual models on the unrestricted design space $[\underline{d}, \overline{d}]$, while under scenario (B) only designs with the actual dose levels are considered. Consequently, the resulting designs under scenarios (A) and (B) might not be ordered with respect to their efficiencies as could be expected otherwise. This is also true under scenario (C): If the five given dose levels were the only feasible ones, we would obtain a maximin design, which has larger efficiencies than those under scenarios (A) and (B) because these are calculated in the class of designs with only four dose levels. Consider now the Bayesian designs in the lower half of Table III. We observe that that the Bayesian designs yield larger efficiencies for the Beta, $\mathrm{E}_{\max}$ and Logistic model, while the smallest efficiency is obtained in the linear model. It is also noteworthy that in the Bayesian case the designs derived under scenario (A) and (C) coincide.

We now focus on the the remaining question about the total number of patients to be included in the dose finding study. Current practice suggests to base the sample size calculation on some power calculation to detect a true treatment effect [23]. Broadly speaking, the responses at the different dose levels d_i are fixed and the probability to achieve a significant dose response signal at study end is calculated for a given suitable test procedure. Another approach is to focus on the dose estimation problem, using a pre-specified minimum precision for the target dose estimate to calculate the sample size, as discussed now.

One possibility to quantify the precision is to pre-specify the expected width of a confidence interval for the target dose estimate of interest, such as given in (3) for the MED estimation problem, and by backward calculation determine the number n of patients required to achieve this expected value. Assume, for example, that the $\mathrm{E}_{\max 1}$ model specified in Table I is the

Scenario	Design specification					Relative efficiencies				
	d_1, w_1	d_2, w_2	d_3, w_3	d_4, w_4	d_5, w_5	Linear	Beta	$E_{max\,1}$	$E_{max\,2}$	Logistic
Maximin design										
(A)	0	47.66	176.82	452.21	500	0.5727	0.5727	0.5727	0.6755	0.5727
	0.356	0.197	0.224	0.056	0.167					
(B)	0	62.5	125	250	500	0.6097	0.6097	0.6097	0.6097	0.6663
	0.286	0.236	0.134	0.103	0.241					
(C)	0	47.66	176.82	452.21	500	0.6315	0.6315	0.6315	0.6853	0.6315
	0.318	0.259	0.178	0.009	0.236					
Bayesian design with $\alpha_i = 0.2$										
(A)	0	45.86	182.1	433.63	500	0.4494	0.6091	0.5921	0.6990	0.7247
	0.384	0.192	0.270	0.035	0.119					
(B)	0	62.5	125	250	500	0.4674	0.5706	0.7635	0.7763	0.7543
	0.322	0.181	0.197	0.144	0.156					
(C)	0	45.86	182.1	433.63	500	0.4494	0.8962	0.6092	0.8193	0.8092
	0.384	0.192	0.270	0.035	0.119					

Table III. Left column: Maximin (top) and Bayesian (bottom) designs for several scenarios (details given in the text). Right column: Relative efficiencies compared to the optimal designs for each model from Table I.

true underlying model and that we consider applying the optimal design $\xi^*_{\text{MED}}(E_{max\,1})$ from Section 3.2. If we require the width of the expected confidence interval for the MED estimate to be less or equal than 100 μg (and thus cover 20% of the dose range under investigation), then $n = 520$ patients are necessary, which are allocated according to the weights $w_i = n_i/n$ determined by $\xi^*_{\text{MED}}(E_{max\,1})$. While such an approach is helpful to communicate the idea of justifying a sample size based on a pre-specified precision, in practice the resulting confidence intervals are likely to be wider because of model uncertainty. Bootstrap methods can be used to obtain confidence intervals, which account for this additional variability.

Another possibility to quantify the precision is to simulate a large number of clinical trials based on the initial assumptions, estimate the target dose at each simulation run, and report the resulting empirical distribution of the dose estimates. To illustrate such an approach, Figure 3 displays the histograms of MED estimates for the dose response models specified in Table I based on 230 observations allocated equally to the actual dose levels and applying the MCP-Mod procedure [10]. Note that for these plots the estimated MED values were rounded to the next dose investigated in the study. Clearly, there is considerable variability in the estimated values, depending on the true dose response shape, how well the true MED is

captured by the doses under investigation, the total sample size and its allocation, etc. We believe that considerations like those described here help the clinical teams to better compare different experimental designs and understand the implications of the individual options.

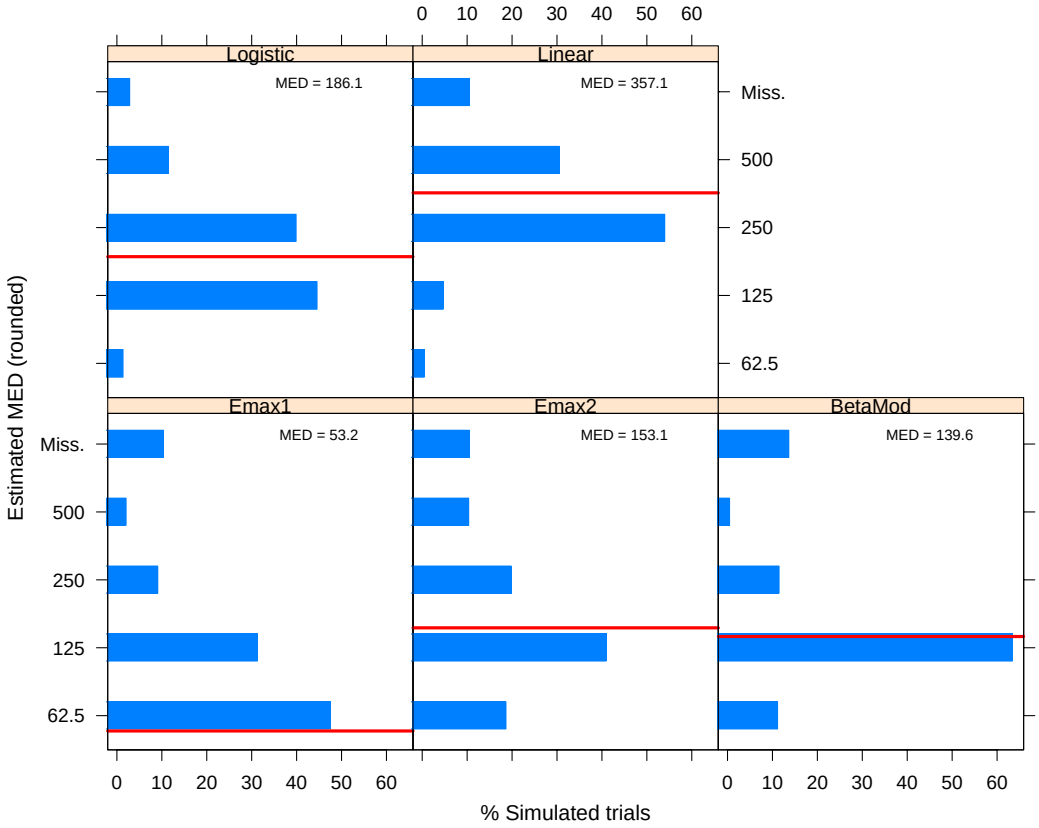

Figure 4. Histograms of MED estimates for the dose response models specified in Table I. Horizontal lines indicate the position of the true MED under a particular model.

5. Discussion

In this paper we summarized MED-, ED_p- and D-optimal designs for common classes of dose response models. The results can be extended to other estimation problems and regression models. The asymptotic designs have generally good finite sample properties and are moderately robust with respect to an initial misspecification of the model parameters. However, the designs are considerably sensitive to a misspecification of the dose regression model. If a clinical team decides to apply a local optimal design for a particular dose response model, it

should be aware of the inherent risks, in case that the true underlying dose response model is different to the assumed one. If the information on the dose response model is too vague, robust designs based on maximin or Bayesian optimality criteria are a viable alternative. Other approaches exist as well to minimize the impact of model uncertainty. Discrimination designs have been investigated, which allow for a differentiation between several non-linear regression models [24, 25]. Response-adaptive designs allow for interim looks during an ongoing study, use the accumulated information to correct the initial assumptions and design the subsequent stages of the trial accordingly [17, 26, 27]. Future research will be devoted to apply these methods and compare the results with those obtained here.

However the decision on the final study design looks like, we believe that a careful investigation of its properties at the planning stage is essential. In this paper we focused on some of the related practical considerations. Computing relative efficiencies for different design options and having a basic notion about the expected precision for the estimation problem will help to understand the inherent implications. With such tools, clinical study designs can be tailored to the specific study objectives and consequently guarantee a higher chance for a successful outcome.

ACKNOWLEDGEMENTS

We thank Yimeng Lu for providing us the case study and for continuing discussions during the progress of this work. We are also grateful to M. Bevanda and A. Pepelyshev for computational assistance. The work of H. Dette was partially supported by the Deutsche Forschungsgemeinschaft (SFB 475: Komplexitätsreduktion in multivariaten Datenstrukturen, Teilprojekt A2), the BMBF project SKAVOE and a NIH grant award IR01GM072876:01A1.

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