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Practical considerations for optimal designs in clinical dose finding studies

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SUMMARY

A key objective in the clinical development of a medicinal drug is the determination of an adequate dose level and, more broadly, the characterization of its dose response relationship. 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 relevant target doses. We consider optimal designs for estimating both the minimum effective dose and the dose achieving a certain percentage of the maximum treatment effect. 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.

Keywords

robust designs; model uncertainty; minimum effective dose; dose estimation

1. Introduction

There are varying degrees of consequences associated with selecting a “wrong” dose level during the drug development process. For example, after having marketed a specified dose of a drug it may become 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 settings 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. The selection of dose level(s) for the confirmatory studies, and hence for potential release on the market, is thus a key decision involving serious ethical and financial consequences. For a recent discussion of issues and challenges arising in clinical dose finding studies we refer to [2].

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The importance of properly conducted dose response studies is reflected by 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*". 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 relevant response that can be declared statistically significantly different from placebo response [1]. The MED can be estimated using either modeling approaches [4] or multiple testing strategies [5, 6]. The maximum useful dose, beyond which no further beneficial effect is seen, can similarly be estimated using multiple testing strategies [7] or modeling approaches when estimating the smallest dose achieving 100p% of the maximum treatment effect in the observed dose range (ED_p, $0 < p < 1$) [8].

As suggested by the quote above, study designs allowing 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 producing 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 either the MED or the ED_p. Given a fixed total number of patients, we determine the necessary number of dose levels, their location within the dose range under investigation, and the proportion of patients allocated to each dose level, such that the asymptotic variance of the target dose estimate is minimized.

The methods 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 possibly additional financial and logistical costs associated with the resulting optimal designs (larger total number of dose levels, the need for producing additional dose levels not considered in previous studies, etc.) against the benefit of an increased information value resulting from larger precision in target dose estimation. The relative efficiencies can be directly translated into relative sample size requirements and are thus easy to communicate to clinical teams and decision boards. Second, asymptotic confidence intervals for target doses can be constructed, which give quantifiable information on the uncertainty about the dose estimate under a particular dose response model. In fact, current practice dictates that sample sizes are calculated based on power requirements to detect dose response. The resulting sample sizes, however, are often inappropriate for estimating a target dose with a reasonable precision. Pre-specifying the width of the confidence interval for a 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 might not be realistic, the methods in this paper can be used to quantify the uncertainty about the target dose estimate, so that the decision makers can better balance the costs and risks based upon the available information. In the remainder of this paper, we formalize these ideas and emphasize practical considerations.

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

This example refers to a real Phase II study for the asthma indication. The primary objective is to support selection of a dose for the Phase III 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). The primary efficacy endpoint is the change from baseline after 14 days of treatment in forced expiratory volume measured over one second,

FEV_1. A placebo effect of 60 mL is assumed with a maximum expected treatment effect increase over placebo response 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 placebo response is considered clinically irrelevant.

At the design stage, the clinical team was unsure about the true dose response shape and could in particular not rule out a non-monotonic profile (such as 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, 9] for details on the use of candidate models in dose response studies and the elicitation of best guesses for the model parameters.

The choice of the dose response models in Table I is tailored to the dose finding study considered here. Many other non-linear regression functions could have been employed instead [10]. One may also argue in favor of using a single, flexible model characterizing a large variety of dose response shapes, such as the four-parameter logistic or sigmoidal E_{max} model [11]. However, such an approach may involve at least two problems: (i) most dose response studies include less than five doses, in which case a model fit with four parameters often leads to numerical convergence problems; (ii) even the four-parameter logistic or sigmoidal E_{max} models do not cover exhaustively the dose response space as they miss, for example, umbrella shapes with downturns at higher doses. Here, we follow the principle of parsimony and use candidate models with a relatively small number of parameters to address model uncertainty.

The uncertainty about the true, but unknown dose response model at the design stage of the study can be seen in Figure 1. The candidate models cover essentially the entire space of potential dose response shapes, including two different parameter specifications for the E_{max} model and an umbrella shape (through the beta model) to cover potential down-turns in effect at larger doses. The potential impact of model uncertainty becomes evident, when comparing the MED across the candidate models. For example, the MED is 53.2 μg for the first E_{max} model, but 357.1 μg for the linear model. 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 advisable because of the uncertainty about the true model and the potential impact on the dose estimates. Given these considerations, the question is how to determine the number of dose levels k, the individual dose levels $d_1, \ldots, d_k$, the allocation ratio at each dose level, and the total sample size n. In Section 3 we discuss methods to address these questions and illustrate the results in Section 4 when re-visiting the case study.

3. Efficient designs for target dose estimation

In this section we consider D-optimal designs for a given dose response model as well as c-optimal designs minimizing the variance of MED or ED_p estimates. We use the E_{max} model 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

$$Y_{ij} = f(d_i, \vartheta) + \varepsilon_{ij} = \vartheta_0 + \vartheta_1 f^0(d_i, \vartheta^0) + \varepsilon_{ij}, \quad (1)$$

where Y_{ij} denotes the response of patient j at dose d_i, $i = 1, \ldots, k$, $j = 1, \ldots, n_i$, and ε_{ij} the residual errors, assumed as independent and normal distributed with common variance σ^2. Further, $f(d, \vartheta)$ denotes the true, but unknown dose response model determined through the parameter vector $\vartheta = (\vartheta_0, \vartheta_1, \vartheta^0)^T = (\vartheta_0, \vartheta_1, \ldots, \vartheta_\ell)^T \in \mathbb{R}^{\ell+1}$, where a^T denotes the transpose of a vector a. Note that we assume f to be partially linear, which applies to commonly used dose response models. When discussing optimal designs below, we will often refer only to the standardized, non-linear function $f^0(d_i, \vartheta^0)$. Example model specifications for the function $f(d, \vartheta)$ are given in Table I.

Let $\underline{d}$ ($\bar{d}$) denote the lowest (highest) dose within the dose range $[\underline{d}, \bar{d}]$ under investigation, where in most cases $\underline{d} = 0$ is the placebo dose (there may be exceptional active-controlled studies, where $\underline{d} > 0$). For a given clinically relevant effect Δ and a model $f(d, \vartheta)$, the MED is defined as

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

The MED does not always exist, as no dose in $(\underline{d}, \bar{d}]$ may produce an improvement of Δ over $f(\underline{d}, \vartheta)$. We restrict the MED to lie within the interval $(\underline{d}, \bar{d}]$ in order to avoid problems arising from extrapolating beyond the dose range under investigation. We estimate the MED by

$$\widehat{\mathrm{MED}} = \inf \{d \in (\underline{d}, \bar{d}] : f(d, \hat{\vartheta}) \geq f(\underline{d}, \hat{\vartheta}) + \Delta\}, \quad (2)$$

where $\hat{\vartheta}$ denotes the non-linear least squares estimate of ϑ. Other estimates for the MED are available. For example, [15] required that the MED is significantly better than placebo. They included the condition $L_d > f(\underline{d}, \hat{\vartheta})$ in (2), where L_d denotes the lower $1 - \gamma$ confidence bound for the expected value $f(d, \hat{\vartheta})$ at dose d. As this estimate leads asymptotically to the same design optimization problem as (2), we do not consider it further. Sometimes, optimization is restricted to a finite set of dose levels, which essentially reduces the design problem to finding the optimal patient allocation to the fixed dose levels $d_1, \ldots, d_k$. We investigate this problem when re-visiting the case study in Section 4. Finally, conditions on higher doses are sometimes imposed, such as the requirement that all doses higher than the MED have to be effective as well. Such conditions are rather strong and not always met in practice (e.g. if umbrella shapes with downturns at higher doses occur); see [2] for further details.

Let $h(d, \vartheta) = f(d, \vartheta) - f(\underline{d}, \vartheta)$ denote the effect difference at $d \in (\underline{d}, \bar{d}]$ and $\underline{d}$. Following [2], we define the ED_p as

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

where $d_{\max} = \mathrm{argmax}_{d \in (\underline{d}, \bar{d}]} h(\underline{d}, \vartheta)$ denotes the dose corresponding to the maximum effect difference in the interval $(\underline{d}, \bar{d}]$. We estimate ED_p by

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

where $\hat{d}_{\max} = \text{argmax}_{d\in(\underline{d},d]} \hbar(d, \hat{\vartheta})$. Including the significance condition $L'_d > 0$ leads asymptotically to the same design optimization problem, where L'_d denotes the lower $1 - \gamma$ confidence bound for the expected value $h(d, \vartheta)$ at dose d. Interestingly, the ED_p does not depend on the parameters for the linear model $f(d, \vartheta) = \vartheta_0 + \vartheta_1 d$ and estimation becomes obsolete, i.e. $\text{ED}_p = \widehat{\text{ED}}_p = \underline{d} + p(\overline{d} - \underline{d})$. From a design perspective any design is thus optimal for estimating the ED_p in the linear model.

Finally, let

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

denote an experimental design with relative patient allocation w_i at dose d_i, $i = 1, \dots, k$. Following [13], the weights $w_i \geq 0$, with $\sum_{i=1}^{k} w_i = 1$, are not necessarily multiples of $1/n$. In practice, for a given total 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 further define 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

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

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 precision measure 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 ϑ.

An optimal design minimizes an appropriate functional of the matrix $M(\xi, \vartheta)$, which is called optimality criterion in the design literature. Although analytical results exist in some cases, most designs have to be determined numerically. Table II summarizes the models and criteria considered in this paper, for which an analytical solution of the design problem can be derived. All optimal designs derived in this section are locally optimal designs in the sense of [12] and require an initial guess of the unknown parameters. Application of these designs is well justified in Phase II studies, where prior information is often available; see also the discussion in Section 2.

3.2. Optimal designs for MED estimation

Using Elfving's theorem [14], Dette et al. [15] investigated optimal designs to estimate the MED for several practically 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 and to illustrate the basic concepts, we focus on the $\text{E}_{\max}$ model

$$f(d, \vartheta) = \vartheta_0 + \vartheta_1 \frac{d}{\vartheta_2 + d}. \quad (3)$$

Here, ϑ_0 denotes the placebo effect, ϑ_1 the asymptotic maximum treatment effect achieved at an infinite dose, and ϑ_2 the ED_{50} [4]. The motivation to focus on the E_{max} model is its ubiquitous use in clinical practice. For example, it can be justified on the relationship of drug-receptor interactions and therefore deduced from the chemical equilibrium equation [16].

We consider first the gradient $g(d, \vartheta) = (1, d/(d + \vartheta_2), -\vartheta_1 d/(d + \vartheta_2)^2)^T$ of $f(d, \vartheta)$ with respect to ϑ for the E_{max} model (3). Figure 2 plots the partial derivatives as a function of the dose d for the two E_{max} models specified in Table I. The $E_{max\,1}$ model, which has smaller ϑ_2 (= ED_{50}) value and steeper increase to the plateau level, has considerably larger values for the first derivatives at smaller doses than the $E_{max\,2}$ model. This will be reflected in the calculation of optimal designs accounting for the dose ranges with the potentially largest amount of information.

The variance of the MED-estimate $\widehat{\mathrm{MED}}$ for a general dose response model f is given by $\sigma^2\Psi_{\mathrm{MED}}(\xi, \vartheta)/n$, where $\Psi_{\mathrm{MED}}(\xi, \vartheta) = b^T(\vartheta_0, \ldots, \vartheta_2)M^-(\xi, \vartheta)b(\vartheta_0, \ldots, \vartheta_2)$, M^- denotes a generalized inverse matrix and the vector b denotes the gradient of the function $f^{-1}\left(\frac{\Delta}{\vartheta_1}+f(\underline{d}, \vartheta)\right)$ with respect to ϑ [15]. For the E_{max} model (3) we have

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

A design ξ^*_{MED} is called MED-optimal if it minimizes $\Psi_{\mathrm{MED}}(\xi, \vartheta)$ among all designs ξ for which the MED is estimable. Such optimal designs can be calculated explicitly for common dose response models with 2 or 3 model parameters; otherwise, numerical optimization methods have to be used [15]. For the E_{max} model (3) the optimal design ξ^*_{MED} is either a two-point or a three-point design, depending on - loosely speaking - the relative position of the MED: If the 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. Note that if a two-point design is optimal for the E_{max} model, the non-trivial support point matches the expected MED. Consequently, the optimal designs for the two E_{max} models specified in Table I are given by

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

The second support point d_2 is considerably smaller for the $E_{max\,1}$ than for the $E_{max\,2}$ model, which is consistent with Figure 2. In practice, two-point designs are insufficient to estimate an E_{max} model, which has 3 parameters and thus requires at least three support points. In such situations we recommend using 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 [15], one can also derive analytical expressions for the variance of $\widehat{\mathrm{MED}}$ under the optimal design ξ^*_{MED}, see Table II for the expressions. Applying these formulas to our numerical example from Table I, we obtain $\Psi_{\mathrm{MED}}\,(\xi^*_{\mathrm{MED}}, \vartheta)=2.77$ for the $\mathrm{E}_{\mathrm{max}\,1}$ model and $\Psi_{\mathrm{MED}}\,(\xi^*_{\mathrm{MED}}, \vartheta)=13.82$ for the $\mathrm{E}_{\mathrm{max}\,2}$ model.

In addition, we can calculate an (asymptotic) confidence interval for the MED. Relying on large sample normal approximations and Slutsky's Theorem, the asymptotic $(1-a)100\%$ confidence interval is

$$\left[\widehat{\mathrm{MED}} - z_{1-\frac{\alpha}{2}}\widehat{\sigma}\sqrt{\frac{\Psi_{\mathrm{MED}}\,(\xi,\widehat{\vartheta})}{n}};\widehat{\mathrm{MED}} - z_{1-\frac{\alpha}{2}}\widehat{\sigma}\sqrt{\frac{\Psi_{\mathrm{MED}}\,(\xi,\widehat{\vartheta})}{n}}\right], \quad (4)$$

where $z_{1-a/2}$ denotes the $1-a/2$ quantile of the standard normal distribution. Optimal designs ξ^*_{MED}, which minimize $\Psi_{\mathrm{MED}}(\xi, \vartheta)$, 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 $a = 0.05$ and assume a total of $n = 100$ patients, we obtain the expected confidence intervals [−60.92; 167.32] for the $\mathrm{E}_{\mathrm{max}\,1}$ and [−101.89; 408.09] for the $\mathrm{E}_{\mathrm{max}\,2}$ model. As expected, the $\mathrm{E}_{\mathrm{max}\,1}$ model allows one to estimate the MED more precisely than the $\mathrm{E}_{\mathrm{max}\,2}$ model, since it is considerably steeper around the expected MED. The large width of the confidence intervals is remarkable, which in case of the $\mathrm{E}_{\mathrm{max}\,2}$ model covers almost the entire dose range under investigation. In Section 4 we discuss how to calculate the necessary sample size for a dose finding study to meet a pre-specified precision of $\widehat{\mathrm{MED}}$ based on (4).

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 $\sigma^2\Psi_{\mathrm{ED_p}}(\xi, \vartheta)/n$, where $\Psi_{\mathrm{ED_p}}(\xi, \vartheta) = c^T(\vartheta_0, \ldots, \vartheta_\ell)M^-(\xi, \vartheta)c(\vartheta_0, \ldots, \vartheta_\ell)$, $M(\xi, \vartheta)$ is 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 $\Psi_{\mathrm{ED_p}}(\xi, \vartheta)$ among all designs ξ. Using Elfving's theorem [14], such optimal designs can be calculated analytically for common dose response models with 2 or 3 model parameters; otherwise, numerical optimization methods have to be used [17]. It can be shown that the vector $c(\vartheta)$ depends neither on ϑ_0 nor on ϑ_1 and consequently is of the form $c(\vartheta) = \gamma(0, 0, c_2, \ldots, c_{\ell-1})^T$ for some constant γ. This implies that ED_p-optimal designs do not depend on p for dose response models with 3 parameters.

As before, we use the $\mathrm{E}_{\max}$ model (3) to illustrate the explicit expressions. We have

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

and the optimal design $\xi^*_{\mathrm{ED}_p}$ is given by

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

where

$$d(\vartheta)=\frac{\vartheta_2\underline{d}+\vartheta_2\overline{d}+2\overline{d}\underline{d}}{2\vartheta_2+\underline{d}+\overline{d}} \quad (5)$$

does not depend on p [17]. The support points in (5) coincide with those for the MED-optimal design if the latter has three dose levels (see Table II). Applying (5), the optimal designs for the two 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 $0 < p < 1$. The second support point d_2 is considerably smaller for the $E_{max\ 1}$ than for the $E_{max\ 2}$ model, which is consistent with the previous findings for the MED estimation problem. Although the ED_p-optimal design does not depend on p, this quantity enters in the asymptotic variance of $\widehat{\mathrm{ED}_p}$ under the ED_p-optimal design $\xi^*_{\mathrm{ED}_p}$, see Table II.

Figure 3 plots $\sqrt{\Psi_{\mathrm{ED}_p}(\xi^*_{\mathrm{ED}_p}, \vartheta)}$ as a function of p for the two E_{max} models specified in Table I. For most $p \in (0, 1)$, the $E_{max\ 1}$ model leads to considerably smaller variances of $\widehat{\mathrm{ED}_p}$ than the $E_{max\ 2}$ model. Recall from Section 3.2 the values $\Psi_{\mathrm{MED}}(\xi^*_{\mathrm{MED}}, \vartheta)=2.77$ for the $E_{max\ 1}$ model and $\Psi_{\mathrm{MED}}(\xi^*_{\mathrm{MED}}, \vartheta)=13.82$ for the $E_{max\ 2}$ 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 $E_{max\ 2}$ model for all $p \in (0, 1)$. The same is true for the $E_{max\ 1}$ model when $p < 0.75$. Note that the maximum value of $\Psi_{\mathrm{ED}_p}(\xi^*_{\mathrm{ED}_p}, \vartheta)$ is numerically the same for both E_{max} models in Figure 3. Finally, asymptotic confidence intervals for the ED_p can be constructed similar to (4).

3.4. D-optimal designs for dose response estimation

So far we investigated c-optimal designs to minimize the variance of either $\widehat{\mathrm{MED}}$ or $\widehat{\mathrm{ED}_p}$. One may argue that optimal designs for one target dose are inefficient for another target dose. Instead, D-optimal designs may be considered, which operate on the determinant of the information matrix $M(\xi, \vartheta)$ and minimize the volume of the confidence ellipsoid for the model parameters, thus focusing on the entire dose response relationship rather than on a single dose [11]. Closed form expressions can often be derived by standard arguments using the equivalence theorem for D-optimality [18], such as for the linear and the E_{max} model. For the other models considered in Table I, D-optimal designs have to be determined numerically.

It can be shown that for the E_{max} model (3) the D-optimal design is

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

where $d(\vartheta)$ is defined in (5). The support points of ξ^*_{D} coincide with those for the ED_p-optimal design [17]. This indicates that for the E_{max} model D-optimal designs are rather efficient to estimate the ED_p and vice versa. For the two E_{max} models specified in Table I, we obtain

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

We now investigate the relative performance of MED-, ED$_p$- and *D*-optimal designs. Relative efficiencies can be calculated that are proportional to the sample size needed for a given design ξ to achieve the same precision as a reference design. If, for example, the relative efficiency of ξ^* versus ξ is 0.5, the optimal design ξ^* would need only half of the patients to achieve the same precision, leading to $100(1-\sqrt{0.5})\% \approx 30\%$ shorter confidence intervals (e.g. for MED or ED$_p$). For our purposes, the relative efficiencies are defined by

$$\mathrm{eff}_{\mathrm{D}}(\xi) = \sqrt[3]{\frac{|M(\xi,\vartheta)|}{\left|M\left(\xi^*_{\mathrm{D}},\vartheta\right)\right|}}, \mathrm{eff}_{\mathrm{ED}_p}(\xi) = \frac{\Psi_{\mathrm{ED}_p}\left(\xi^*_{\mathrm{ED}_P},\vartheta\right)}{\Psi_{\mathrm{ED}_p}(\xi,\vartheta)}, \quad \text{and} \quad \mathrm{eff}_{\mathrm{MED}}(\xi) = \frac{\Psi_{\mathrm{MED}}\left(\xi^*_{\mathrm{MED}},\vartheta\right)}{\Psi_{\mathrm{MED}}(\xi,\vartheta)}.$$

In Table III we use the $\mathrm{E}_{\max 1}$ model to show the efficiencies of the different designs; the efficiencies for the $\mathrm{E}_{\max 2}$ model are similar and therefore omitted. The MED-optimal design is supported at only two points and does not allow estimation of all model parameters. We therefore use the modified design $\tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 1})$ from Section 3.2, allocating 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$_p$. This is because the ED$_p$ is difficult to determine as it depends both on the target and the maximum response.

Relative efficiencies can also be used to investigate the behavior of optimal designs when the initial model parameters have been misspecified. For example, if in the MED estimation problem the true parameters for the $\mathrm{E}_{\max}$ model are given $\rho_1 = 300$ and $\rho_2 = 25$, the slightly modified optimal design $\tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 1})$ calculated under the assumption that the parameters are given by $\vartheta_1 = 294$ and $\vartheta_2 = 25$ has 88% efficiency for estimating the MED. This calculation can be extended to perform a sensitivity analysis by systematically investigating a variety of scenarios. Table IV summarizes the efficiency results $\mathrm{eff}_{\mathrm{MED}}(\tilde{\xi}^*) = \Psi_{\mathrm{MED}}(\xi^*_{\mathrm{MED}},\rho)/\Psi_{\mathrm{MED}}(\tilde{\xi}^*,\vartheta)$ for selected values of $\rho = (\rho_1, \rho_2)$, where $\tilde{\xi}^* = \tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 1})$ for short. The local MED-optimal design $\tilde{\xi}^*_{\mathrm{MED}}(\mathrm{E}_{\max 1})$ remains very efficient for a broad range of parameter values ρ_1 and ρ_2. Robustness with respect to misspecification of the initial model parameters has also been reported elsewhere [9, 15].

3.5. Robust designs

All 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. Dette et al. [15] investigated the robustness of MED-optimal designs with respect to their assumptions and concluded that locally optimal designs are moderately robust with respect to a misspecification of the model parameters, but highly sensitive to a misspecification of the regression function.

We recommend using model robust designs in practice, which are less sensitive to the choice of the regression model. The following considerations are generic and hold for robustifying either MED-, ED$_p$-, or D-optimal designs. 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 [19, 20] to aggregate this information. We illustrate the relative performance of both types of robust design when revisiting 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 standardized 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 $f_j(d, \vartheta^{(j)})$ specified through the parameters $\vartheta^{(j)}$ with associated optimal designs ξ_j^*, $j = 1,\ldots,m$, a design is called standardized 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 corresponding optimal design. The standardized 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 maximize the weighted sum $\sum_{j=1}^m \alpha_j \log \text{eff}_j(\xi)$, leading to so-called compound optimal designs. The model probabilities may reflect the clinical team beliefs 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 compound design for subsequent cohorts of patients. Such flexibility is not available for standardized maximin designs.

Following [21, 22], we combine the different optimality criteria through efficiencies instead of optimality criteria depending directly on the information matrices. The reason is that for a given design the values of a particular criterion are usually of different magnitude for different models. For example, it is indicated in [15] that the variance of $\widehat{\text{MED}}$ in the $E_{\max}$ model is at least twice as large than the corresponding variance in the logistic model. Consequently, if these quantities would be used in a compound or maximin criterion for these two models, the resulting robust design would be dominated by the MED-optimal design for the $E_{\max}$ model and have poor properties for estimating the MED in the logistic model. The consideration of efficiencies avoids this problem, because the value of a criterion for each model is calculated relatively to the best value, which could be obtained by the choice of an experimental design. We refer to [21] for further discussion regarding standardized optimal 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. Recall the open design questions, that is, the determination of the number of dose levels k, the individual dose levels $d_1,\ldots, d_k$, the allocation ratio at each dose level, and the total sample size n. Given the inherent model uncertainty problem, we calculate both maximin and compound 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 model. In practice, the choice of 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 $[\underline{d}, \bar{d}]$ can be investigated in a clinical study. In the current study, such logistical considerations let the clinical team randomizing the patients to the four active dose levels 62.5, 125, 250, and 500 μg and placebo (denoted in the following as *actual* dose levels and indicated by open dots in Figure 1). Since restricting the space of admissible doses impacts the final design choice, we consider maximin and compound designs for both the unrestricted and the restricted case:

- **A.** Unrestricted search for a robust design over the continuous interval $[\underline{d}, \bar{d}] = [0, 500]$.
- **B.** Search restricted to the actual dose levels 0, 62.5, 125, 250, and 500 μg.
- **C.** Search restricted to the dose levels obtained in (A).

For scenarios (B) and (C) the design search is restricted to determine the allocation ratios w_i for the given dose levels.

Table V provides the results for the six different cases. Consider first the maximin designs in the upper half of Table V. Allowing for an unrestricted design search in $[\underline{d}, \bar{d}]$ under scenario (A), the maximin design is a five-point design, allocating roughly 36%, 20%, 22%, 6% and 16% of the patients to the dose levels 0, 49, 177, 452 and 500 μg, respectively. The right columns in Table V give the efficiency of the maximin design relative to the optimal designs for each model on the unrestricted design space. If we restrict the design search to the actual dose levels, we obtain the results given under scenario (B). The relative efficiencies under scenario (B) are uniformly smaller than those under scenario (A), because we are not optimizing with respect to the dose levels. The standardized maximin optimal designs from strategy (C) differ to those from strategy (A), because the locally optimal designs for the individual models (which are required for the efficiency calculations) are different in both cases.

Similar conclusions hold for the compound designs in the lower half of Table V. For scenario (A), the compound designs lead to larger efficiencies for the beta, E_{max} and logistic model as compared to the maximin designs, while the smallest efficiency is obtained for the linear model. Note that the designs derived under scenarios (A) and (C) coincide because we used logarithms of the efficiencies in the definition of the compound optimality criterion. Consequently, the locally optimal designs for the individual models have no impact on the optimization problem.

Optimal or robust designs are often not directly applicable in practice, because either the resulting dose levels are “odd” and not feasible in practice or the allocation weights are unrealistic. For example, in practice it would be difficult to follow the recommendation for scenario (C) in the upper half of Table V and allocate 0.9% of the patients to dose 452.21 μg. Instead, robust or optimal designs should be considered as benchmarks, to which other, practically feasible designs can be compared. In addition, constraints on the minimum number of patients can be incorporated, thus ensuring a minimum weight w_i for each dose d_i. Continuing the example with the 0.9% allocation, one could require that, for example, at least 5% of the patients are allocated to each dose, i.e. $w_i \geq 0.05$. This gives the new weights 0.327, 0.219, 0.210, 0.050, and 0.194 for the dose levels $d_1, \ldots, d_5$, respectively.

We now focus on the remaining question about the total number of patients for the dose finding study. Current practice suggests that the sample size is based on power calculations to detect a true treatment effect [9]. 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 (4) for the MED estimation problem, and by backward calculation determine the number n of patients required to achieve this value. Assume, for example, that the $E_{max\,1}$ model specified in Table I is the true underlying model and that we apply the optimal design $\xi^*_{\mathrm{MED}}\,(\mathrm{E}_{\max\,1})$ from Section 3.2. If we require the width of the expected confidence interval for the MED estimate to be less than or equal to 100 μg (and thus cover 20% of the dose range under investigation), then n = 520 patients are necessary and allocated according to the weights $w_i = n_i/n$ determined by $\xi^*_{\mathrm{MED}}(\mathrm{E}_{\max\,1})$. 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 too short because of model uncertainty. Bootstrap methods can be used to obtain confidence intervals accounting for this additional variability.

Another possibility to quantify the precision is simulating a large number of clinical trials based on initial assumptions, estimate the target dose at each simulation run, and report the resulting empirical distribution of the dose estimates. Figure 4 displays the histograms of MED estimates for the dose response models in Table I based on equally allocating 230 patients to the actual doses and applying the MCP-Mod procedure described in [23]. 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 such considerations help the clinical teams to better compare different experimental designs and understand the implications of the individual options.

5. Discussion

In this paper we presented MED-, ED_p- and D-optimal designs for common 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 regression model. From a drug development perspective, model uncertainty is a key characteristic and cannot be underestimated. Thus, if a clinical team decides to apply locally 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 not the assumed one. If the information on the dose response model is too vague, we instead recommend using robust designs to address model uncertainty. By construction, such designs are not optimal for any single dose response model, but lead to an overall high efficiency. We described robust designs based on standardized maximin or compound optimality criteria as a viable alternative to optimal designs for a single dose response model. Other approaches are available to minimize the impact of model uncertainty. Optimal discrimination designs have been investigated, that allow differentiating among several non-linear regression models [24, 25]. Response-adaptive designs have also been proposed, which 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 [11, 26, 27]. Future research will be devoted to apply these methods and compare the results with those obtained here.

Further considerations beyond those discussed in this paper may become relevant when applying optimal designs in clinical dose finding studies. Phase III studies are often

conducted with a dose that has already been used in Phase II, which limits the choice of dose levels for Phase II studies. In particular, the MED is not necessarily the dose to be continued in Phase III. But its estimation provides important information as to the lower bound of all useful doses: any dose smaller than the MED can be discarded, because it does not provide sufficient clinical effect. The final decision, which doses to carry forward into Phase III often includes aspects beyond the efficacy of the drug under investigation. Safety considerations are particularly important and we refer to [28] for optimal designs accounting for both efficacy and safety. A similarly important consideration is the inclusion of covariates at the design stage. For example, it is common practice to perform covariate-adjusted analyses in clinical trials where the response is change from baseline and the baseline value is included as a covariate. It would be an interesting topic of further research to investigate optimal designs accounting for covariates, which have not been observed at the planning stage of a clinical study.

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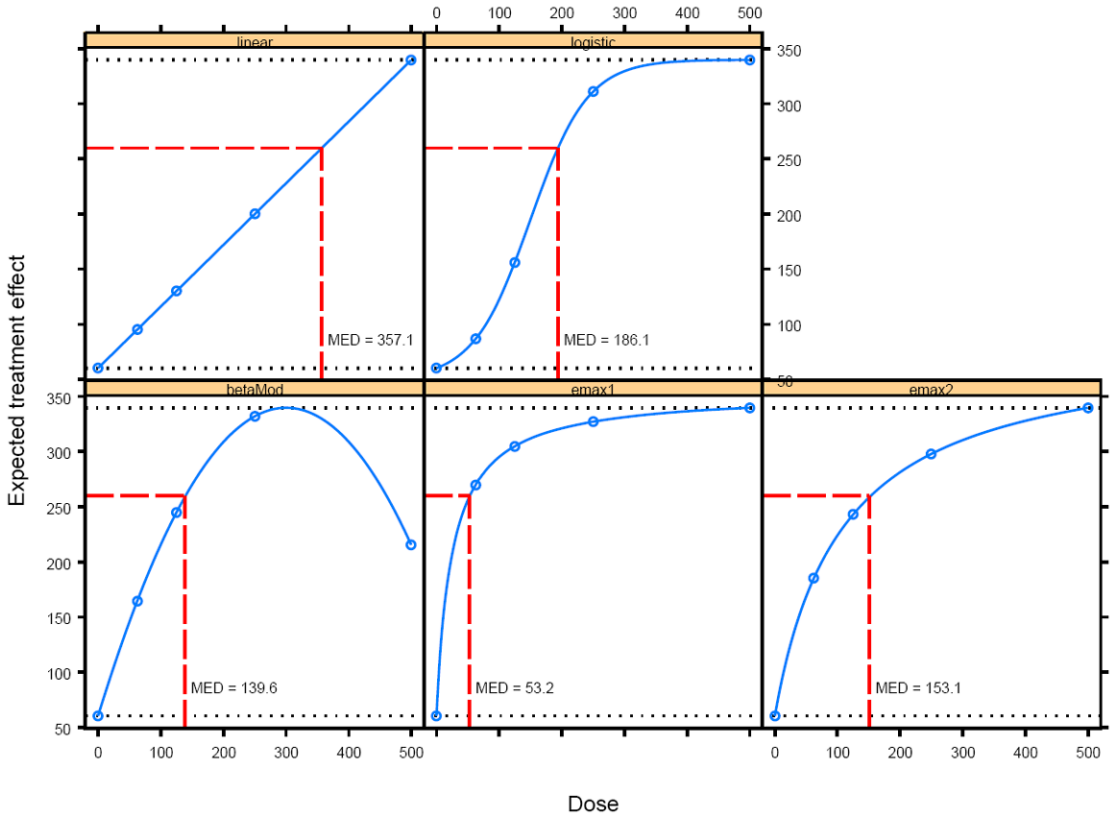

Figure 1.
Graphical display of the dose response models from Table I. Open dots indicate the dose levels actually used in the study (0, 62.5, 125, 250, and 500 μg). Horizontal dashed line: clinical relevance threshold Δ on top of placebo response.

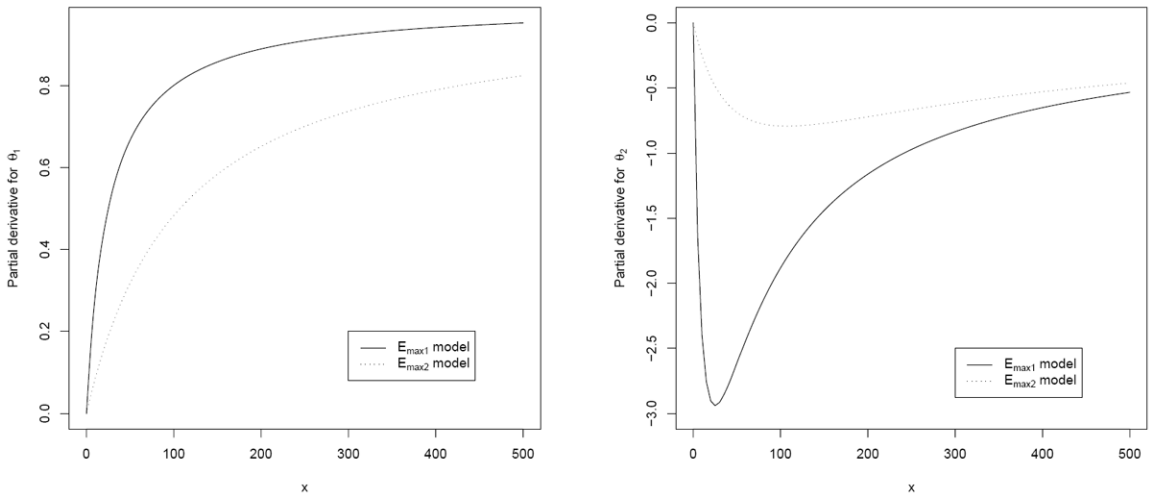

Figure 2.
Partial derivatives for the two E_{max} models specified in Table I. Left plot: $d/(d + \vartheta_2)$; right plot: $-\vartheta_1 d/(d + \vartheta_2)^2$.

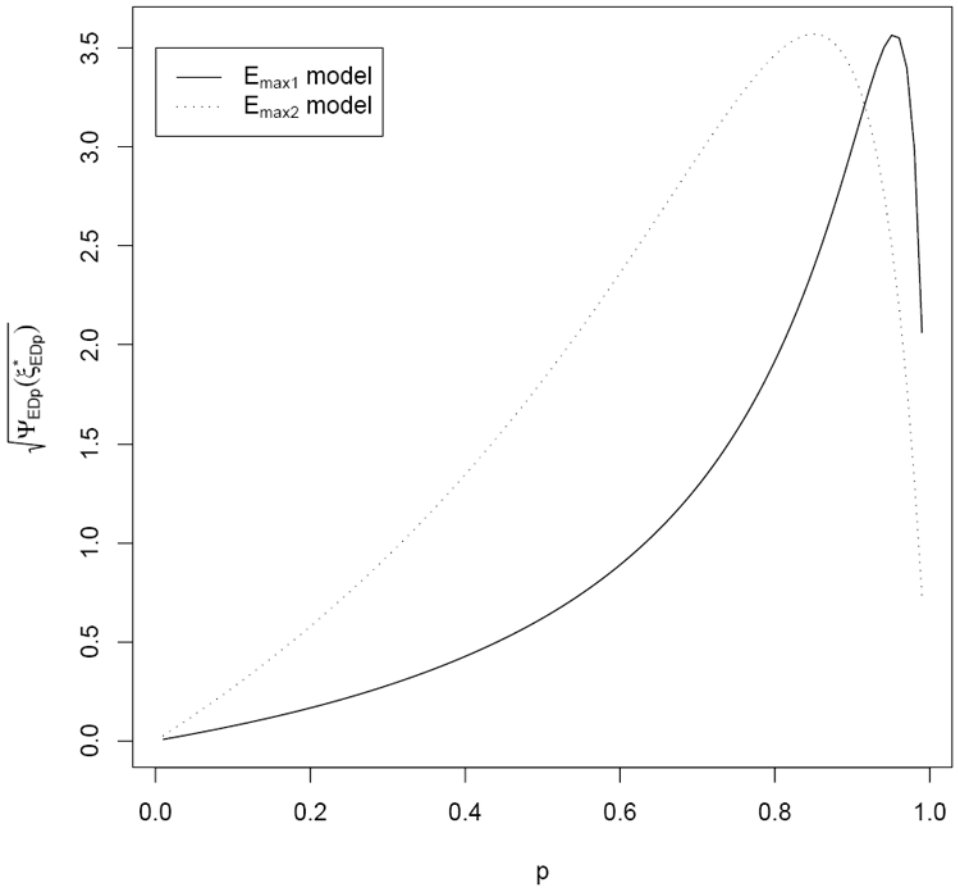

Figure 3.

The function $\sqrt{\Psi_{\mathrm{ED}_p}(\xi^*_{\mathrm{ED}_p}, \vartheta)}$ for the two E_{max} models specified in Table I.

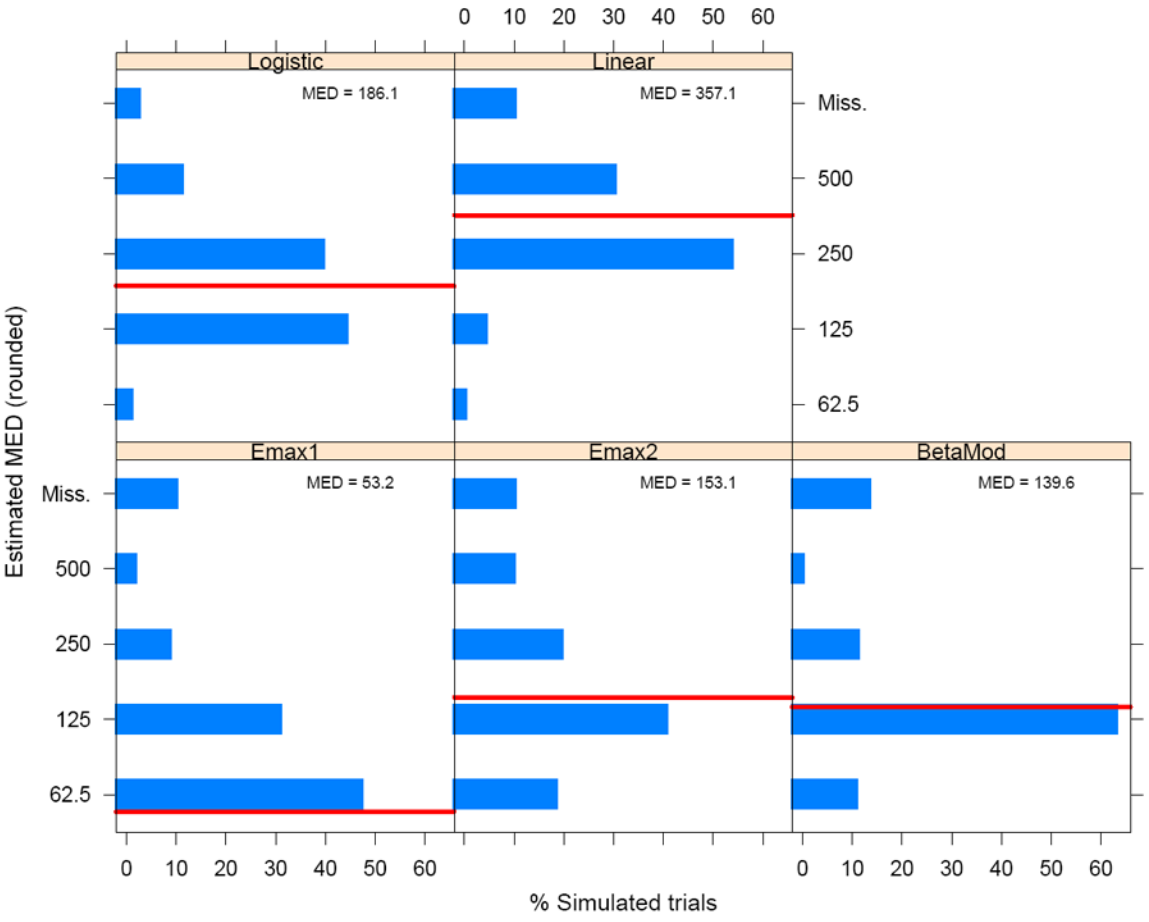

Figure 4.
Histograms of MED estimates for the dose response models specified in Table I. Horizontal lines indicate the position of the true MED under a particular model. “Miss.” gives the proportion of simulations, where the MED could not be estimated.

Table I

Candidate dose response models as a function of dose d. For the beta model $B(\alpha, \beta) = (\alpha + \beta)^{\alpha+\beta}/(\alpha^{\alpha} \times \beta^{\beta})$.

Model	Full model specification	Parameter $\vartheta = (\vartheta_0, \ldots, \vartheta_\delta)$
linear	$\vartheta_0 + \vartheta_1 d$	(60, 0.56)
beta	$\vartheta_0 + \vartheta_1 B(\vartheta_2, \vartheta_3)(d/\vartheta_4)^{\vartheta_2}(1 - d/\vartheta_4)^{\vartheta_3}$	(60, 280, 1, 1, 600)
$E_{max\ 1}$	$\vartheta_0 + \vartheta_1 d/(\vartheta_2 + d)$	(60, 294, 25)
$E_{max\ 2}$	$\vartheta_0 + \vartheta_1 d/(\vartheta_2 + d)$	(60, 340, 107.14)
logistic	$\vartheta_0 + \vartheta_1/\{1 + \exp[(\vartheta_2 - d)/\vartheta_3]\}$	(49.62, 290.51, 150, 45.51)

Table II

Optimal designs for the linear regression and E_{max} model for various optimality criteria. The quantity Δ^* is defined by $\Delta^* = \vartheta_1\vartheta_2\,(\overline{d} - \underline{d})/\{2(\underline{d} + \vartheta_2)(\underline{d} + \vartheta_2)\}$, while the quantity $w(\vartheta_2)$ is given by $w(\vartheta_2)=1/4 - (\overline{d} - \underline{d})\vartheta_2\vartheta_1/\{8[(\overline{d} - \underline{d})\vartheta_2\vartheta_1+\Delta\vartheta_2(\underline{d}+\overline{d})+\Delta(\vartheta_2^2+\overline{d}\underline{d})]\}$.

	linear	**variance**	**E_{max}**	**variance**
D	$\begin{pmatrix} \underline{d} & \overline{d} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$	n.a.	$\begin{pmatrix} \underline{d} & \frac{(\overline{d}+\vartheta_2)\underline{d}+(\underline{d}+\vartheta_2)\overline{d}}{2\vartheta_2+\underline{d}+\overline{d}} & \overline{d} \\ \frac{1}{3} & \frac{1}{3} & \frac{1}{3} \end{pmatrix}$	n.a.
ED_p	any	0	$\begin{pmatrix} \underline{d} & \frac{(\overline{d}+\vartheta_2)\underline{d}+(\underline{d}+\vartheta_2)\overline{d}}{2\vartheta_2+\underline{d}+\overline{d}} & \overline{d} \\ \frac{1}{4} & \frac{1}{2} & \frac{1}{4} \end{pmatrix}$	$\frac{\sigma^2}{n}\left(\frac{8p(1-p)(\vartheta_2+\underline{d})^2(\vartheta_2+\overline{d})^2}{\vartheta_1\vartheta_2(\vartheta_2+p\underline{d}+(1-p)\overline{d})^2}\right)^2$
MED $\Delta < \Delta^*$	$\begin{pmatrix} \underline{d} & \overline{d} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$	$\frac{2\sigma^2\,\Delta^2}{n\vartheta_1^4(\underline{d}^2+\overline{d}^2)}$	$\begin{pmatrix} \underline{d} & \frac{(\overline{d}+\vartheta_2)\underline{d}+(\underline{d}+\vartheta_2)\overline{d}}{2\vartheta_2+\underline{d}+\overline{d}} & \overline{d} \\ w(\vartheta) & \frac{1}{2} & \frac{1}{2}-w(\vartheta) \end{pmatrix}$	$\frac{\sigma^2}{n}\frac{4\vartheta_1^2\vartheta_2^2(\underline{d}+\vartheta_2)^4}{(\vartheta_1\vartheta_2-\Delta(\underline{d}+\vartheta_2))^4}$
MED $\Delta > \Delta^*$	$\begin{pmatrix} \underline{d} & \overline{d} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$	$\frac{2\sigma^2\,\Delta^2}{n\vartheta_1^4(\underline{d}^2+\overline{d}^2)}$	$\begin{pmatrix} \underline{d} & \frac{\vartheta_2(\Delta\vartheta_2+(\Delta+\vartheta_1)\underline{d}}{\vartheta_2\vartheta_1-\Delta(\underline{d}+\vartheta_2)} \\ \frac{1}{2} & \frac{1}{2} \end{pmatrix}$	$\frac{8\sigma^2}{n}\frac{\Delta^2(\underline{d}+\vartheta_2)^6(\overline{d}+\vartheta_2)^2\left\{(\underline{d}-\overline{d})\vartheta_1\vartheta_2+\Delta(\vartheta_2+\underline{d})(\vartheta_2+\overline{d})\right\}^2}{\vartheta_2^2\vartheta_2^4(\overline{d}-\underline{d})^4(\Delta(\underline{d}+\vartheta_2)-\vartheta_1\vartheta_2)^2}$

n.a. = not available

Table III

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

Design	Relative efficiency		
	$\mathbf{eff_D(\xi)}$	$\mathbf{eff_{ED_p}(\xi)}$	$\mathbf{eff_{MED}(\xi)}$
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 IV

The efficiency of the design $\tilde{\xi}^{*}_{\mathrm{MED}}\,(\mathrm{E}_{\max 1})$ with respect to misspecification of the initial parameters under the $\mathrm{E}_{\max}$ model for the MED estimation problem.

ρ_1	270	280	290	300	310	320
ρ_2	19	21	23	25	27	29
efficiency	0.91	0.89	0.88	0.88	0.87	0.87

Table V

Left column: Maximin (top) and compound (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.

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	0.5727	0.4318	0.4875	0.6113	0.4182
	0.286	0.236	0.134	0.103	0.241					
(C)	0	47.66	176.82	452.21	500	0.5727	0.4382	0.5613	0.6293	0.5045
	0.318	0.259	0.178	0.009	0.236					
Compound design with $\alpha_i = 0.2$										
(A)	0	45.86	182.1	433.63	500	0.4494	0.6091	0.5921	0.7247	0.6990
	0.384	0.192	0.270	0.035	0.119					
(B)	0	62.5	125	250	500	0.4494	0.4734	0.4513	0.7132	0.3714
	0.322	0.181	0.197	0.144	0.156					
(C)	0	45.86	182.1	433.63	500	0.4494	0.6091	0.5921	0.7247	0.6990
	0.384	0.192	0.270	0.035	0.119					