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Optimal designs for composed models in pharmacokinetic–pharmacodynamic experiments

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Abstract

We consider two frequently used PK/PD models and provide closed form descriptions of locally optimal designs for estimating individual parameters. In a novel way, we use these optimal designs and construct locally standardized maximin optimal designs for estimating any subset of the model parameters of interest. We do this by maximizing the minimal efficiency of the estimates across all relevant parameters so that these optimal designs are less dependent on the individual parameter or parameters of interest. Additionally, robust designs are proposed to further reduce the dependence on the nominal values of the parameters. We compare efficiencies of our proposed optimal designs with locally optimal designs and designs used in four real studies from the literature and show that our proposed designs provide advantages over those used in practice.

Keywords

Pharmacokinetic/pharmacodynamic experiments; Approximate design; D-optimal design; Estimating individual parameters; Equivalence theorem; Maximin optimal design; Robust design

Introduction

Many papers in the pharmaceutical literature do not discuss the rationale of their designs and some examples of such papers are given in “Comparison with designs used in practice” section. A few researchers in the field have led painstaking efforts to use more informed designs for PK/PD studies over the years and it appears that they have been successful, judging from the increased attention in design issues for PK/PD studies in recent years, see [2, 12, 20], for example. Indeed, pharmacometricians seem to have taken a unique lead in terms of putting together websites to generate optimal designs and perform analysis for their

models. We know of at least four groups from different countries that have established websites for finding optimal designs. Dr. F. Mentre from the University of Paris Diderot in France have PFIM with codes written in R and the website is at <http://www.pfim.biostat.fr/>. Another program is PopDes written in Matlab by Dr. K. Ogungbenro from the University of Manchester, UK. The website address is <http://www.pharmacy.manchester.ac.uk/capkr/popdes/>. Professors J. Nyberg, S. Ueckert and A. Hooker from University of Uppsala in Sweden also have a program called PopED written in Matlab and housed at <http://www.poped.sourceforge.net>. Still another program called WinPOPT/POPT is available at <http://www.winpop.com/>. The codes are in Matlab and its owner is Professor S. Duffull from the University of Otago in New Zealand. These websites all have a common focus on PK/PD models with some overlapping capabilities and several results from these separately developed websites have been compared and validated. There are still some that do not explicitly have a website but their codes are available upon request. One example is the program PKstamp written in MATLAB code by Drs. S. Leonov and A. Aliev. All these websites generally generate designs for random effects models but they can be used to find optimal designs for fixed-effect models by setting the variances of the effects to zero or to a very small positive value. Examples of software that provide *D*-optimal designs for fixed effects nonlinear models are S-Adapt and WinNonLin. Additionally, optimal designs can be found using the procedure NLINMIX in the general statistical program SAS, where codes for analyzing population models are also available. Programs for analyzing fixed effects models are available in statistical packages such as SAS and STATA, among others.

Nonlinear models are widely employed in PK/PD studies, see for example, [19, 31], just to name a couple. A popular choice is compartmental models that comprise sum of exponential terms to model plasma concentration time course [30]. There is increasing interest to study the pharmacokinetic and pharmacodynamic properties of a drug by combining the PK and PD models to form a PK/PD model and estimate parameters in the PK/PD model simultaneously. Other advantages of a PK/PD model are given in [10] where they found locally *D*-optimal design for two PK/PD models. Our specific interest here is to use theory and construct locally optimal designs, standardized maximin optimal designs and robust optimal designs for the Emax/mono-compartment and Emax/effect-compartment models. The latter two types of designs are increasingly proposed and studied for linear and simple nonlinear models in the statistical literature, starting with [5]. The potential use of maximin designs for PK models seems to be picking up as well [11]. In the present paper, we apply such techniques to design a PK/PD model rather than a PK model and a PD model separately. Specifically, we introduce robust designs for PK/PD models and demonstrate their advantages over designs currently used in practice. Our results suggest that the proposed maximin optimal designs and robust designs can serve as compelling alternatives and complementary designs in drug studies.

Locally optimal designs are the simplest to determine for a nonlinear model. They were proposed by [3] and they require nominal values for the parameters be available before they can be implemented. Nominal values come from pilot studies, experts' opinion or related studies. Locally optimal designs usually represent a first step to build more complex designs, as we exemplify in "Optimality criterion" section. Given the nominal values, a design can be

verified to be locally optimal using an equivalence theorem, which is available when the design criterion is a convex functional of the information matrix [21]. The equivalence theorem gives us a practical way of verifying whether a design is optimal by plotting the directional derivative of the criterion evaluated at that design over the time interval. Illustrative examples of such plots in bio-pharmaceutical studies are given in [13, 35].

It is well known that locally optimal designs can strongly depend on the nominal values, see for example [6, 8]. This means that small mis-specifications in the nominal values can result in very different optimal designs. A more concrete example of such a situation can be seen in Table 1 in “Emax/mono-compartment model” section, where a small mis-specification in the nominal values of the parameters results in a very different optimal design. The locally optimal design for estimating θ_1 alone does not depend on θ_1 and θ_2 and depends only on θ_3 and θ_4 . In the second and third rows of Table 1, we have $\theta_3 = 0.2$, and we observe the locally optimal design for estimating θ_1 changes dramatically from a singular design requiring all observations at the $T = 120$ to a 4-point design when θ_4 changes from 0.05 to 0.10. Consequently, a locally optimal design constructed under one set of nominal values can become inefficient when another set of nominal values is assumed. Robust designs were introduced in [5, 18] as a way to reduce the dependence on the nominal values. In the simplest case, they maximize the minimum of efficiencies that may arise from mis-specification of the nominal values. In the same spirit, minimax optimal designs minimize the worst possible loss from mis-specification of the nominal values. In either the minimax or maximin approach, we need to specify a plausible region for all possible values of the model parameters before we optimize. This is usually accomplished by specifying a plausible interval for each parameter. Consequently, this approach is appealing because it does not require practitioners to specify a single best guess or a prior distribution for the values of the parameters of interest. However, minimax or maximin optimal designs are notoriously difficult to find due to technical difficulties and they defy analytical description, except for the simplest problems. Wong [33] provided an overview of theoretical design issues for minimax optimality criteria and Dette [5] provided yet another compelling rationale for use of such optimal designs in practice.

In the next section, we discuss two popular PK/PD models and in “Optimality criterion” section, we define two maximin design criteria. The maximin approach begins by assigning an index to each model parameter of interest to form an index set, say J . If there are k parameters in the model and all the k parameters in the model are of interest, we set $J = \{1, 2, 3, \dots, k\}$. If only parameters 2 and 4 are of interest, then $J = \{2, 4\}$. For a given set of nominal values, we next determine the locally optimal design for estimating each of the parameters in the index set J and calculate the efficiencies of an arbitrary design for estimating each parameter in J . The standardized maximin optimal design sought is the one that provides the maximal minimum of the efficiencies among all designs.

The standardized maximin optimal design still depends on the nominal values and so they are only locally optimal. One may extend the above optimization by specifying an interval that contains plausible values for each parameter. The plausible region for optimization now comprises the set J and the plausible interval for each parameter of interest. We call the resulting maximin standardized optimal design a robust design because this design

maximizes the minimum of the set of efficiencies for estimating parameters in the set J and also over the plausible interval for each parameter in J .

The present paper is organized as follows. “PK/PD models” section describes our models and “Optimality criterion” section discusses optimality criteria. “PK/PD models” section contains results for the Emax/mono-compartment model and presents locally optimal designs for estimating each parameter in the model, standardized maximin optimal designs and robust designs. We also study locally D -optimal designs which minimize the volume of the confidence ellipsoid for all the parameters in the model and they are widely used for estimating all model parameters. We report their efficiencies relative to our proposed designs. “Emax/effect-compartment model” section presents corresponding results for the Emax/effect-compartmental model. In “Comparison with designs used in practice” section, we evaluate efficiencies of four designs used in practice relative to our proposed designs and demonstrate the advantages of our proposed designs. We offer a summary in “Summary” section and an appendix that contains justifications for our results.

PK/PD models

We consider the nonlinear regression model given by

$$y_{i,l} = \eta(t_{i,l}, \theta) + \varepsilon_{i,l}, \quad l=1, \dots, n_i, \quad i=1, \dots, n, \quad (1)$$

where $y_{i,l}$ is an observation from the i th subject at time $t_{i,l} \in [0, T]$, errors $\varepsilon_{i,l}$ are independent and identically distributed random variables with zero mean and variance $\sigma^2 > 0$ and $N = \sum_i n_i$ is the sum of the number of measurements from all subjects. We recognize our independence assumption may be contrived but we feel the design ideas proposed herein are appealing and extension to the case with correlated responses seems possible using ideas somewhat based on new design techniques in [34]. In the present paper we focus on the fixed-effect model. Design issues for some nonlinear random-effect models can be found in [7, 17] among others.

A PK/PD model is obtained by composing a PK model and a PD model, that is

$$\eta(t, 0) = \eta_{PD}(\eta_{PK}(t, \theta^{PK}), \theta^{PD}),$$

where the vector of model parameters is given by $\theta = (\theta^{PD}, \theta^{PK})$. For the PD model $\eta_{PD}(C, \theta^{PD})$ the traditional model choice is the Emax model

$$\eta_{PD}(C, \theta^{PD}) = \theta_1^{PD} + \frac{\theta_2^{PD} C}{\theta_3^{PD} + C}$$

where $\theta^{\text{PD}} = (\theta_1^{\text{PD}}, \theta_2^{\text{PD}}, \theta_3^{\text{PD}})^T$, θ_1^{PD} is the baseline effect (placebo), $\theta_1^{\text{PD}} + \theta_2^{\text{PD}}$ is the maximal effect related to the drug, θ_3^{PD} is the plasma concentration producing 50 % of the maximal effect, and C is a concentration [24, 32].

The choice of a PK model depends on the particular application. We consider two commonly used models in the present paper. One is the mono-exponential model or a single compartment model given by

$$\eta_{\text{PK}}(t, \theta^{\text{PK}}) = D_1 e^{-t\theta_1^{\text{PK}}},$$

where θ_1^{PK} is the plasma clearance (or the elimination rate constant) and the other is the effect compartment model given by

$$\eta_{\text{PK}}(t, \theta^{\text{PK}}) = D_1 \frac{\theta_2^{\text{PK}}}{\theta_2^{\text{PK}} - \theta_1^{\text{PK}}} \left(e^{-t\theta_1^{\text{PK}}} - e^{-t\theta_2^{\text{PK}}} \right).$$

The parameter θ_1^{PK} is the elimination rate constant and the parameter θ_2^{PK} is the absorption rate constant. In both models, D_1 is Dose/ V , where Dose is a known constant and V is the unknown apparent volume of the distribution to be estimated. The actual dose for each subject is $D_1 V$ and the parameter D_1 is assumed to be known in the present paper. More details for these and other PK models are given in [9, 27] and, in textbooks, such as [26, 28].

Optimality criterion

We assume that we are allowed to take a total of N observations for the study and N is pre-determined either from cost constraints. The design problem is how to obtain the N observations in some optimal fashion over a period of time and across subjects. Following convention, we formulate our optimality criterion in terms of the Fisher information matrix. The Fisher information matrix for the general nonlinear model defined in (1) is

$$M(\xi_N, \theta) = \sum_{i=1}^n \sum_{l=1}^{n_i} f(t_{i,l}) f^T(t_{i,l}), \quad f(t) = f(t, \theta) = \frac{\partial \eta(t, \theta)}{\partial \theta},$$

$\xi_N = \{t_{1,1}, \dots, t_{n,n_n}\}$, and the inverse of $M(\xi_N, \theta)$ is asymptotically proportional to the covariance matrix of the nonlinear least squares estimator of the parameter θ . An optimal design minimizes or maximizes a statistically meaningful functional of the information matrix.

An exact design requires the specification of each time point for each subject in the study. Because the optimization of the information matrix for exact designs is extremely difficult, we reformulate the problem and work with approximate designs. These approximate designs are essentially discrete probability measures defined over the study time period. If w_i is the

proportion of subjects in the study with observations at t_i , $i = 1, \dots, r$, we denote such a design by $\xi = \{t_1, t_2, \dots, t_r; w_1, w_2, \dots, w_r\}$. With a total of N observations in the study, we implement the approximate design by first rounding each Nw_q up or down so that it is an integer s_q and subject to $s_1 + \dots + s_r = N$. The implemented design then takes s_q observations at time points t_q , $q = 1, \dots, r$. In practice, the number of subjects to be included in the study is typically fixed either by past experience on the number that can be realistically recruited into the study given the time frame or by cost. This implies that if $N = 100$ and we plan to recruit 10 subjects, then the above approximate design ξ tells us to take about $10w_i$ observations at r time point t_i 's and where these time points are.

Approximate designs are much easier to find and study than exact optimal designs and they perform just as well as exact optimal designs even when the sample sizes are moderate [22]. More importantly, when the design criterion is convex over the space of information matrices, computer algorithms are available for generating many types of optimal approximate designs.

Following convention, we use the Fisher information matrix of design ξ to measure the worth of a design. This matrix is defined by

$$M(\xi, \theta) = \sum_{q=1}^r w_q f(t_q) f^T(t_q),$$

see [21]. For a given statistical model and a design criterion, the design problem consists of selecting the optimal number r of time points to use in the study, the optimal sampling time points $t_1, \dots, t_r$ and the corresponding optimal proportions $w_1, \dots, w_r$ of observations to sample from these time points.

We focus on design criteria that provides some global protection to our estimates regardless which parameter or parameters are of interest after the design is completed. Our design criterion is more sophisticated and as will be seen, more flexible than the traditional criteria as well. As a motivation, consider for example, the sigmoid Emax model frequently used to characterize the concentration-response curve in part because of its flexibility and ease of interpretation of the four parameters; see [15]. Three of the four parameters represent mean responses at the zero dose, at the maximal dose and at a dose mid-way between the minimum and maximum treatment effect. Researchers may not know at the design stage which of the latter two dose levels are of particular interest and, consequently, the goal then is to use a maximin optimal design to estimate the two parameters so that both parameters will be estimated with the highest possible efficiency regardless which parameter is more interesting second on. Another motivation for the design criterion is that some parameters in the model are biologically more important than others but it is still not possible to tell in advance which of these is more or less more interesting among the biologically important ones.

For estimating a single parameter, we want to construct a design that accurately estimates $c^T \theta$, where $c = e_j$ and e_j is the vector with the j th entry equals to one and other entries equal

to zero. Such an optimal design minimizes the variance of the estimate of the j th parameter among all designs. When all the parameters of interest are represented in the set J , we want a design that maximizes the minimal efficiency for estimating the selected parameters. This means that for a given nominal value θ , we want to find a design that maximizes

$$\Psi_m(\xi, \theta) := \min_{j \in J} \{\text{eff}_j(\xi, \theta)\} \quad (2)$$

among all approximate designs ξ on $[0, T]$,

$$\text{eff}_j(\xi, \theta) = \frac{e_j^T M^-(\xi_{e_j}^*, \theta) e_j}{e_j^T M^-(\xi, \theta) e_j},$$

and $\xi_{e_j}^*$ is the locally e_j -optimal design for estimating the j th parameter, i.e. the design $\xi_{e_j}^*$ that minimizes the asymptotic variance of the estimate of the parameter θ_j given by

$$e_j^T M^-(\xi, \theta) e_j. \quad (3)$$

The minimization of the criterion (3) is performed over all designs ξ such that $e_j \in \text{range } M(\xi, \theta)$. Note that we have used $M^-(\xi, \theta)$ to denote a generalized inverse of the Fisher information matrix because the information matrix of an optimal design may be singular. We note that in most PK studies all parameters are of interest and in this case the set J in the criterion (2) is chosen as the full index set. Our more general formulation can be useful to PK/PD models and also to models that have nuisance parameters.

Following [5, 18] we call a design maximizing the criterion (2) a standardized maximin optimal design. Such optimal designs have a maximin type of criteria and it is well known such optimal designs are notoriously difficult to construct. Except for the simplest models with a single optimality criterion, these optimal designs have to be determined numerically and in a computationally burdensome manner. Fortunately, our technical results in Lemma 2 or Lemma 3 given in the appendix show that the standardized maximin optimal designs for the Emax/mono-compartment model and Emax/effect-compartment model do not depend on θ_1 and θ_2 . This simplifies the computational burden for finding standardized maximin optimal designs considerably.

Clearly, standardized maximin optimal designs still depend on nominal values of the model parameters that we try to estimate and so they are only locally optimal. To reduce the dependence on the nominal values, we introduce a robust optimality criterion and define a robust design as the design that maximizes

$$\Psi_R(\xi) := \min_{j \in J} \min_{\theta \in \Omega} \{\text{eff}_j(\xi, \theta)\} \quad (4)$$

for a user-selected plausible set Ω for the unknown model parameters. In practice, the set Ω is a cartesian product of the plausible intervals specified for each parameter. The robust designs provide an additional level of protection against mis-specification of unknown values of the model parameters. The robust designs achieve their aim by maximizing the minimal efficiency of the parameter estimates over the set of all parameters of interest and also the given plausible region of values for the selected parameters.

We compute standardized maximin and robust designs using an iterative algorithm. First, we maximize the optimality criterion within the class of all s -point designs where the initial value of s we choose is the number of parameters in the model. We call the resulting design a s -point standardized maximin optimal design. Such designs are typically easier to find numerically than standardized maximin optimal designs, which have no restriction on the number of design points in the optimization problem. We employ the Nelder–Mead algorithm in the MATLAB package for optimization. After the optimal s -point standardized maximin design is found, we consider the class of all $(s + 1)$ -point designs and find an optimal design within this class and repeat the procedure. At each iteration, we increase the number of points by one, until no reduction in the criterion value is observed.

Emax/mono-compartment model

Locally optimal designs for estimating individual parameter

The Emax/mono-compartment model is given by

$$\eta(t, \theta) = \theta_1 + \frac{\theta_2}{\theta_3/D_1 e^{\theta_4 t} + 1} \quad (5)$$

where $\theta = (\theta_1, \theta_2, \theta_3, \theta_4)^T$ and the explanatory variable t varies in a user-selected interval $[0, T]$. Without loss of generality we put $D_1 = 1$. A direct calculation shows that the gradient of the regression function is

$$f(t) = f(t, \theta_2, \theta_3, \theta_4) = \left(1, \frac{1}{\theta_3 e^{\theta_4 t} + 1}, \frac{-\theta_2 e^{\theta_4 t}}{(\theta_3 e^{\theta_4 t} + 1)^2}, \frac{-\theta_2 \theta_3 t e^{\theta_4 t}}{(\theta_3 e^{\theta_4 t} + 1)^2} \right)^T. \quad (6)$$

We now construct and study properties of the locally e_j -optimal designs over the interval $[0, T] = [0, 120]$. This time interval was chosen because we want to compare our designs with the locally D -optimal designs reported in [10]; likewise we use the same set of nominal values for the parameters employed in their paper.

Table 1 displays locally e_j -optimal designs for estimating each parameter in the model for selected nominal values of parameters θ_3 and θ_4 . It is clear that all optimal designs do not depend on the parameters that enter linearly in the model. For the Emax/mono-compartmental model, these parameters are θ_1 and θ_2 and this explains why nominal values of parameters θ_1 and θ_2 are not given in Table 1. We observe that the locally optimal design for estimating the baseline effect θ_1 (i.e. the e_1 -optimal design) advises the experimenter to take all observations at $t = T$ most of the time. A heuristic explanation is that the Emax/

mono-compartment model defined in (5) has a feature $\lim_{t \rightarrow \infty} \eta(t, \theta) = \theta_1$. In other words, the baseline effect is most efficiently estimated by taking all observations as long as possible after drug administration. An exception is the second parameter setting in Table 1, where the optimal design requires observations at the time points 0, 23.335, 63.612 and 120. We observe that for this particular parameter setting, namely $\theta_3 = 0.2$ and $\theta_4 = 0.05$, the response at $t = T$ is not close enough to the asymptotic value θ_1 .

The above findings on the design characteristics, like in many other such studies, are based on numerical studies. This is because definitive conclusions about robustness properties of optimal designs are invariably hard to obtain for nonlinear models. For the Emax/mono-compartment model, we were able to prove an interesting result in Lemma 2 in the appendix that shows the e_1 , e_2 , e_3 and e_4 -optimal designs all have the same support points. This means that if the goal is to estimate just one parameter in the model, the optimal time points are always the same but the proportions of observations taken at these points may vary depending on the particular parameter is of interest. We will see that this property does not apply to the Emax/effect-compartmental model in the next section.

Locally D -optimal designs are available for the Emax/mono-compartment model in [10]. Table 2 shows their efficiencies relative to the locally optimal designs for estimating the individual parameters. The efficiencies of the locally D -optimal designs for estimating the parameters θ_3 and θ_4 are approximately 82 %, and even higher efficiencies are obtained when we want to estimate the parameter θ_2 . However, they have rather low efficiencies for estimating the baseline effect θ_1 , ranging between 25 and 47 %. This re-emphasizes the message that while locally D -optimal designs are easy to construct and commonly used, their indiscriminate use can result in poor efficiencies if we have a more targeted inference.

Maximin optimal and robust designs for the Emax/mono-compartmental model

This subsection reports maximin optimal and robust designs for the Emax/mono-compartmental model. Table 3 displays standardized maximin optimal designs for selected values of the parameters. The top portion of the table shows the different designs and efficiencies when the minimum in the criterion (2) is taken over all parameters, i.e. $J = \{1, 2, 3, 4\}$. In this case the standardized maximin optimal design yields efficiencies between 56 and 80 %, because it is a compromise between two very different types of designs: the locally optimal design for estimating the baseline effect θ_1 , which puts most of its weight at the right boundary of the time interval and the locally optimal designs for estimating the other parameters θ_2 , θ_3 , θ_4 , which use less observations at the point T . On the other hand, if estimation of the baseline is not of interest, one sets $J = \{2, 3, 4\}$ in (2) and Table 3 shows that the standardized maximin optimal designs for this choice of J are very efficient. Note that neither the optimal designs nor the efficiencies depend on θ_1 and θ_2 .

Similar to the proof of Lemma 2 in the appendix, it can be shown that the robust designs do not depend on the interval limits for the parameters θ_1 and θ_2 . Accordingly, Table 4 shows some robust designs without specifying the interval for θ_1 and θ_2 . The robust designs now have 6 support points which is more than number of parameters in the assumed model and this allows us to check for validity of the mean assumptions among the nested models. Specifically, the test of model adequacy requires that the model with more parameters

contains the model under consideration as a special case when the additional parameters are fixed at some values, typically zero. This hypothesis is then tested by a likelihood ratio test. The right column of Table 4 contains the minimal efficiency, where the minimum is taken over the set J and the plausible region Ω . This value corresponds to the worst case in $J \times \Omega$ for which the efficiency is minimal. For many other values $(j, \theta) \in J \times \Omega$, the efficiencies of the robust design are substantially higher.

Emax/effect-compartment model

Locally optimal design for estimating individual parameter

The Emax/effect-compartment model is given by

$$\eta(t, \theta) = \theta_1 + \frac{\theta_2(e^{-\theta_4 t} - e^{-\theta_5 t})}{\theta_3(1 - \theta_4/\theta_5)/D_1 + (e^{-\theta_4 t} - e^{-\theta_5 t})} \quad (7)$$

where $\theta = (\theta_1, \theta_2, \theta_3, \theta_4, \theta_5)^T$, $t \in [0, T]$ and we use $T = 120$ in the following examples. Without loss of generality we put $D_1 = 1$. A direct calculation shows that the vector of regression functions for the model (7) is

$$f(t) = f(t, \theta_2, \theta_3, \theta_4, \theta_5) = \left(1, \frac{(e^{-\theta_4 t} - e^{-\theta_5 t})\theta_5}{\theta_3(\theta_5 - \theta_4) + \theta_5(e^{-\theta_4 t} - e^{-\theta_5 t})}, \frac{-\theta_2(e^{-\theta_4 t} - e^{-\theta_5 t})\theta_5(\theta_5 - \theta_4)}{(\theta_3(\theta_5 - \theta_4) + \theta_5(e^{-\theta_4 t} - e^{-\theta_5 t}))^2}, \right. \\ \left. - \frac{\theta_2\theta_5\theta_3(te^{-\theta_4 t}(\theta_5 - \theta_4) - e^{-\theta_4 t} + e^{-\theta_5 t})}{(\theta_3(\theta_5 - \theta_4) + \theta_5(e^{-\theta_4 t} - e^{-\theta_5 t}))^2}, \frac{\theta_2\theta_3(\theta_5 te^{-\theta_5 t}(\theta_5 - \theta_4) - e^{-\theta_4 t}\theta_4 + e^{-\theta_5 t}\theta_4)}{(\theta_3(\theta_5 - \theta_4) + \theta_5(e^{-\theta_4 t} - e^{-\theta_5 t}))^2} \right)^T.$$

The construction of the e_j -optimal designs for this model is similar to the method used for the Emax/mono-compartment model. In the appendix, we give some details in Lemma 3, which also provides information on how the optimal design changes when the time interval changes.

Table 5 displays locally e_j -optimal designs for selected nominal values of the parameters. Nominal values for θ_1 and θ_2 are omitted since the optimal designs do not depend on their values. We also list efficiencies of the locally D -optimal designs for estimating the individual parameters in Table 6. It is clear that the locally D -optimal designs yield rather low efficiencies for estimating the individual parameters. This re-emphasizes that while locally D -optimal designs are relatively easy to determine and popular in practice, they are by no means always adequate for estimating a subset of the model parameters. The message is that if there is a single target inference one should design specifically for that inference and not use a general purpose easy to find design.

Maximin optimal and robust designs for the Emax/effect-compartmental model

We pointed out earlier on that standardized maximin designs do not depend on the nominal values of θ_1 and θ_2 and this observation is useful because it simplifies our search of the optimal designs. Standardized maximin optimal designs for the Emax/effect-compartment model for selected values of the model parameters are given in Table 7 and some robust designs are presented in Table 8. Similarly to the situation discussed in Section 4, the

inclusion of the efficiency of estimation of the baseline effect in the optimality criterion (2), i.e. the case when $1 \in J$, reduces the minimal efficiency of the standardized maximin optimal design; see the top portion of Table 7. On the other hand, when we have $J = \{2, 3, 4, 5\}$, the bottom portion of Table 7 shows the standardized maximin optimal designs have at least approximately 75 % efficiencies for estimating the parameters $\theta_2, \theta_3, \theta_4, \theta_5$ in the Emax/effect-compartment model.

Table 8 shows the robust designs and their corresponding minimal efficiencies calculated over the set $J \times \Omega$. Because the set Ω used in the optimality criterion is a very big cuboidal region, the resulting minimal efficiencies are small. However, it should be noted again that these values represent the minimal efficiencies over the set Ω , and at most points in this set, the efficiencies are substantially larger. On the other hand, the minimal efficiency of the robust design is close to the minimal efficiency of standardized maximin optimal design if the set Ω is small. It can be shown that the minimal efficiency (4) of the locally D -optimal designs in Table 6 is approximately 0.01, which is much smaller than the minimal efficiency of the robust designs in Table 8. It is also interesting to note that the values of θ from Table 6 are not equal to the vertices of Ω , where the minimal efficiency is attained. As a consequence, the efficiencies in Table 8 are not smaller than the minimal efficiency in Table 6.

Comparison with designs used in practice

We now provide illustrative examples that resemble experimental studies reported in four papers from the bioscience literature using composed pharmacokinetic-pharmacodynamic models. Our intent here is to demonstrate our methodology and show how to compare performance of designs used in real studies with our robust designs when the assumed model is the Emax/mono-compartment model or the Emax/effect-compartment model. We provide three comparisons using the Emax/mono-compartment model and one using the Emax/effect-compartment model. Specifically, we show designs in real studies can experience a substantial lose in efficiency when the parameters of interest are mis-identified and/or nominal values are mis-specified whereas our robust designs can mitigate these loses.

The four real studies are only briefly described below and we refer reader to the original papers for details. The emphasis here is the design that was implemented in each study.

- (S1) Rosario et al. [25] used a viral dynamics model to compare the effectiveness of in vivo viral inhibition of several doses of maraviroc and used a modeling approach to support design considerations for a monotherapy using different dose regimens of maraviroc. We focus on the sampling time scheme on the last day of treatment where plasma samples were taken at 0, 1, 2, 4, 6, 8, 24, 48, 72 and 120 h postdose for PK measurements. Subjects were asymptomatic HIV-1 infected patients.
- (S2) Agoram et al. [1] described an experiment where PK samples were collected at 0, 0.5, 6, 24, 48, 72, 96, and 120 hours for studying chemotherapy-induced anemia. Subjects were given Darbepoetin Alfa and the aim was to develop and evaluate a population pharmacokinetic–pharmacodynamic model.

- (S3) Danhof et al. [4] used an integrated pharmacokinetic-pharmacodynamic approach to optimize R-apomorphine delivery in patients with idiopathic Parkinson's disease. The sampling scheme was to use equidistant time points in the study.
- (S4) Magee et al. [16] conducted a study to assess lymphocyte responsiveness to immunosuppressive therapy using a three-component complex model to characterize effects of prednisolone. Blood samples were drawn at 0, 1, 2, 4, 6, 8, 12, 18, 24 and 32 hours from healthy volunteers who received a single total body weight-based oral dose of prednisone.

These cited papers did not provide justification for their designs and for easy reference, we denote the approximate design used in each of the above studies respectively by

$$\begin{aligned}\xi_1 &= \{0, 1, 2, 4, 6, 8, 24, 48, 72, 120\}, \\ \xi_2 &= \{0, 0.5, 6, 24, 48, 72, 96, 120\}, \\ \xi_3 &= \{0, 12, 24, 48, 60, 72, 84, 96, 108, 120\}, \\ \xi_4 &= \{0, 1, 2, 4, 6, 8, 12, 18, 24, 32\}.\end{aligned}$$

For simplicity, we assume the range for each nominal parameter for all the four studies is the same and we report them at the top of Tables 4 and 8. We note that the estimated values of parameters in the four studies all fall within the specified ranges. Our purpose here is to compare performance of the implemented designs ξ_1 , ξ_2 , ξ_3 and ξ_4 with our robust designs when parameters of interest are mis-identified and/or nominal values of the parameters are mis-specified. We use the ratio

$$C_j(\xi_r, \xi_i, \theta) = \frac{e_j^T M^{-}(\xi_i, \theta) e_j}{e_j^T M^{-}(\xi_r, \theta) e_j}$$

to measure the efficiency of the design ξ_i for estimating the j th parameter in the model relative to the robust design ξ_r in the i th study. The value C_j can be interpreted as follows. If θ is the “true” set of parameter values for the model, the robust design has C_j times smaller variance for the estimated j th parameter compared with the implemented design ξ_i . This implies if $C_j > 1$ the robust design ξ_r should be preferred; otherwise if $C_j < 1$, the design ξ_i has a smaller variance for the estimated j th parameter and so it is preferred.

The robust design for the i th study is given in the caption of figure i , $i = 1, 2, 3, 4$. The robust designs for the first three studies have 6 design points and the robust design for the fourth study has 7 points. Each figure shows the robustness properties of its robust design ξ_r by displaying the contour plot of the function $C_j(\xi_r, \xi_i, \theta)$ for various values of the parameter θ . We do not change the nominal values of θ_1 and θ_2 because the ratio C_j does not depend on them. All four figures show that for almost all parameter settings of interest, the robust designs yield substantially smaller variances than the designs ξ_1 , ξ_2 , ξ_3 and ξ_4 used in practice.

Figures 1 and 2 show that the variances of the estimated parameters θ_1 , θ_2 , θ_3 , θ_4 from the robust design are on average at least 1.2–1.4 times smaller than the corresponding variances for the designs ξ_1 and ξ_2 , respectively. In terms of confidence interval, the lengths of the confidence intervals for these parameters are shorter using our proposed robust designs. The improvement can be substantial. For example, if the “true” parameters are $\theta_3 = 0.2$ and $\theta_4 = 0.13$, the upper left panel in Fig. 1 shows the variance for the estimated baseline effect θ_1 from the robust design ξ_r is approximately 1.7 times smaller than the variance obtained from the design ξ_1 .

In Fig. 3 we show the corresponding performance of the design ξ_3 used in the Parkinson’s disease study. The variances for the estimated parameters θ_2 , θ_3 , θ_4 obtained from the robust design are on average 1.6 times smaller than the corresponding variances obtained from the design ξ_3 . On the other hand, the commonly used design ξ_3 yields up to 0.75 times smaller variances for the parameter θ_1 in the Emax/mono-compartment model if $\theta_4 > 0.08$ and up to 1.6 times larger variances if $\theta_4 < 0.08$.

Finally, Fig. 4 below displays corresponding results for the robust design for the 5-parameter Emax/effect-compartment model for estimating θ_2 , θ_3 , θ_4 and θ_5 . Similar figures can be constructed to include θ_1 as well. To avoid 3-dimensional contour plots, we construct the plots by fixing $\theta_5 = 0.5$ for an illustrative case. We observe the variances of the estimates of the parameters θ_2 , θ_3 , θ_4 obtained from the implemented design ξ_4 are about on average 2.5 times larger than the corresponding variances obtained from the robust design. The same observation also holds for the parameter θ_5 unless $\theta_4 > 0.08$, in which case the variances from the implemented design for estimating θ_5 is about 0.8 times smaller than those from the robust design.

Summary

Optimal designs for estimating individual parameters or some of the parameters in a linear model are relatively straightforward to find, but the task is much harder for nonlinear models. We provided new and analytical descriptions for locally optimal designs for estimating individual model parameters in two popular PK/PD models—the Emax/mono-compartment and Emax/effect-compartment model. These designs were then used to construct locally standardized maximin optimal designs that are efficient for estimating selected parameters in the model. Robust designs reduce their dependence on a single set of nominal values by allowing each parameter to lie in an interval believed to capture its plausible values.

We constructed locally optimal designs for estimating each parameter, locally standardized maximin and robust optimal designs for the Emax/mono-compartment and Emax/effect-compartment models. Using four real studies from the literature, we showed that robust designs tend to outperform the implemented designs, including the popular uniform design employed in Study 3. In many instances, robust designs outperformed the implemented designs substantially in terms of more precise estimates for the parameters of interest. Another advantage of robust designs is that they typically have more design points than the number of parameters in the model and this allows us to conduct a lack-of-fit test to assess

model adequacy. This is not the case for locally optimal designs where typically the number of design points is the same as the number of parameters in the model.

A limitation of our approach is that we assume errors are independently distributed. This assumption may not be applicable for some studies because responses within patient over a short period of time are likely to be correlated. However, we view our proposed design strategy as an intermediary step to building more efficient and realistic designs. In our future research we are going to expand the current work by constructing optimal designs that account for the correlated responses over time. Indeed the first two authors had just published new design techniques for correlated responses [34] that may have applications to PK/PD models as well.

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Appendix justifications

We first state an auxiliary result for finding locally optimal designs for the two models.

Lemma 1 is a reformulation of the equivalence theorem for e_j -optimality and is useful in the present context; details can be found in [21].

Lemma 1

Let $f(t) = (f_1(t), \dots, f_k(t))^T$ and assume the components are linearly independent continuous functions on the interval $[0, T]$. The design $\xi = \{t_1, t_2, \dots, t_r, w_1, w_2, \dots, w_r\}$ is e_j -optimal for estimating the j^{th} parameter if and only if there exists a vector $q \in \mathbb{R}^k$, such that $q_j \neq 0$ and the generalized polynomial $q^T f(t)$ satisfies the following conditions

- i. $q^T f(t_i) = (-1)^i, i = 1, \dots, k$
- ii. $|q^T f(t)| \leq 1$ for all $t \in [0, T]$
- iii. $Fw = v e_j$

for some $v > 0$, where $F = ((-1)^s f_i(t_s))_1^{\text{PD}}$ and $w^T = (w_1, \dots, w_r)$. Moreover, $e_j^T M^{-1}(\xi) e_j = 1/v^2$.

The next two lemmas form the basis for the construction of the proposed optimal designs. In particular, we show that the functions $f_1(t), f_2(t), f_3(t)$ and $f_4(t)$ appeared in the gradient defined in (6) form a Chebyshev system on the interval $[0, T]$.

Lemma 2

For the Emax/mono-compartment model defined in (5) we have:

1. The locally e_j -optimal designs do not depend on the parameters θ_1 and θ_2 .
2. The locally e_3 - and e_4 -optimal designs are supported at four unique points, $t_1^*, t_2^*, t_3^*, t_4^*$, as solutions of the system of nonlinear equations

$$q_1 + q_2 \frac{1}{\theta_3 e^{\theta_4 t_i} + 1} + q_3 \frac{-\theta_2 e^{\theta_4 t_i}}{(\theta_3 e^{\theta_4 t_i} + 1)^2} + q_4 \frac{-\theta_2 \theta_3 t_i e^{\theta_4 t_i}}{(\theta_3 e^{\theta_4 t_i} + 1)^2} = (-1)^{i-1}, \quad (8)$$

$i = 1, \dots, 4$, with respect to scalar numbers $q_1, \dots, q_4$ and points $t_1, \dots, t_4$ subject to the condition $|q^T f(t)| \leq 1$ for all $t \in [0, T]$. The corresponding weights are given by

$$w^* = \frac{F^{-1} e_j}{\mathbf{1}^T F^{-1} e_j},$$

where $\mathbf{1} = (1, \dots, 1)^T$, $F = (f(t_1^*), -f(t_2^*), f(t_3^*), -f(t_4^*))$, $t_1^* = 0$ and $t_4^* = T$.

3. Let $t_i(\theta_3, \theta_4, T)$ be a point with corresponding weight $w_i(\theta_3, \theta_4, T)$ of the locally e_j -optimal design on the interval $[0, T]$. Then for any $\gamma > 0$ we have

$$\begin{aligned}\gamma t_i(\theta_3, \theta_4, T) &= t_i(\theta_3, \theta_4/\gamma, \gamma T), \quad w_i(\theta_3, \theta_4, T) \\ &= w_i(\theta_3, \theta_4/\gamma, \gamma T).\end{aligned}$$

Proof of Lemma 2

Since $f(t, \theta) = \text{diag}(1, 1, \theta_2, \theta_2) f(t, \theta_3, \theta_4)$ where

$$\tilde{f}(t, \theta_3, \theta_4) = \left(1, \frac{1}{\theta_3 e^{\theta_4 t} + 1}, \frac{-e^{\theta_4 t}}{(\theta_3 e^{\theta_4 t} + 1)^2}, \frac{-\theta_3 t e^{\theta_4 t}}{(\theta_3 e^{\theta_4 t} + 1)^2} \right)^T,$$

the optimality criterion (3) is a product of two functions. The first function depends on the parameter θ_2 but not on the design, while the second function depends on the design but does not depend on the parameters θ_1 and θ_2 . Consequently, we obtain the first statement of the lemma.

By standard arguments it can be shown that functions $\{f_1(t), f_2(t), f_3(t), f_4(t)\}$ form a Chebyshev system on the interval $[0, T]$ and each of the systems $\{f_1(t), f_2(t), f_3(t)\}$ and $\{f_1(t), f_2(t), f_4(t)\}$ is also a Chebyshev system. Therefore, it follows that the optimal designs for estimating the parameters θ_3 and θ_4 are uniquely supported at the Chebyshev points defined by the Eq. (8), even though there are 4 equations and 8 variables in the system of equations; see [14] for more details. The weights can then be determined using results from [23] and this proves the second part of the lemma. The third part of the lemma follows from the fact that

$$f(\gamma t, \theta_2, \theta_3, \theta_4) = \text{diag}(1, 1, 1, \gamma) f(t, \theta_2, \theta_3, \gamma \theta_4).$$

Lemma 3

For the Emax/effect-compartment model defined in (7) we have:

1. The locally e_j -optimal designs do not depend on the parameters θ_1 and θ_2 .
2. The locally e_1 -optimal design is a one-point design supported at the point 0.
3. Let $t_i(\theta_3, \theta_4, \theta_5, T)$ be a point with corresponding weight $w_i(\theta_3, \theta_4, \theta_5, T)$ of a locally e_j -optimal design on the interval $[0, T]$. Then for any $\gamma > 0$ we have

$$\begin{aligned}w_i(\theta_3, \theta_4, \theta_5, T) &= w_i(\theta_3, \theta_4/\gamma, \theta_5/\gamma, \gamma T), \\ \gamma t_i(\theta_3, \theta_4, \theta_5, T) &= t_i(\theta_3, \theta_4/\gamma, \theta_5/\gamma, \gamma T).\end{aligned}$$

Proof of Lemma 3

The first part is obtained using similar arguments in the proof of Lemma 2. The second part directly follows from Lemma 1 with $q = e_1$. The third part follows from the identity

$$f(\gamma t, \theta_2, \theta_3, \theta_4, \theta_5) = \text{diag}(1, 1, 1, \gamma, \gamma) f(t, \theta_2, \theta_3, \gamma \theta_4, \gamma \theta_5).$$

Fig. 1.

Contour plots of the values for $C_j(\xi_r, \xi_1, \theta)$ (6) as θ_3 and θ_4 vary for the implemented design $\xi_1 = \{0, 1, 2, 4, 6, 8, 24, 48, 72, 120\}$ and the robust design $\xi_r = \{0, 7.2, 16.7, 31.0, 60.1, 120; 0.121, 0.139, 0.157, 0.125, 0.108, 0.349\}$ for estimating θ_1 (top left with $j = 1$), θ_2 (top right with $j = 2$), θ_3 (bottom left with $j = 3$), and θ_4 (bottom right with $j = 4$) in the Emax/mono-compartment model (5) in study 1

Fig. 2.

Contour plots of the values for $C_j(\xi_r, \xi_2, \theta)$ (6) as θ_3 and θ_4 vary for the implemented design $\xi_2 = \{0, 0.5, 6, 24, 48, 72, 96, 120\}$ and the robust design $\xi_r = \{0, 7.2, 16.7, 31.0, 60.1, 120; 0.121, 0.139, 0.157, 0.125, 0.108, 0.349\}$ for estimating θ_1 (top left with $j = 1$), θ_2 (top right with $j = 2$), θ_3 (bottom left with $j = 3$), and θ_4 (bottom right with $j = 4$) in the Emax/mono-compartment model (5) in study 2

Fig. 3.

Contour plots of the values for $C_j(\xi_r, \xi_3, \theta)$ (6) as θ_3 and θ_4 vary for the implemented design $\xi_3 = \{0, 12, 24, 48, 60, 72, 84, 96, 108, 120\}$ and the robust design $\xi_r = \{0, 7.2, 16.7, 31.0, 60.1, 120; 0.121, 0.139, 0.157, 0.125, 0.108, 0.349\}$ for estimating θ_1 (top left with $j = 1$), θ_2 (top right with $j = 2$), θ_3 (bottom left with $j = 3$), and θ_4 (bottom right with $j = 4$) in the Emax/mono-compartment model (5) in study 3

Fig. 4.

Contour plots of the values for $C_j(\xi_r, \xi_4, \theta)$ (6) as θ_3 and θ_4 vary for the implemented design $\xi_4 = \{0, 1, 2, 4, 6, 8, 12, 18, 24, 32\}$ and the robust design $\xi_r = \{0, 0.18, 1.81, 5.9, 14.0, 26.9, 53.8; 0.106, 0.115, 0.145, 0.129, 0.118, 0.212, 0.175\}$ for estimating θ_2 (top left with $j = 2$), θ_3 (top right with $j = 3$), θ_4 (bottom left with $j = 4$), and θ_5 (bottom right with $j = 5$) in the Emax/effect-compartment model (7) with an exemplary value of 0.5 for θ_5 in study 4

Table 1

The locally e_j -optimal designs $\{t_1^*, t_2^*, t_3^*, t_4^*; w_1, w_2, w_3, w_4\}$ for the Emax/mono-compartment model defined in (5) for $j = 1, 2, 3, 4$

θ_3	θ_4	t_2^*	t_3^*	e_1 -optimal				e_2 -optimal			
				w_1	w_2	w_3	w_4	w_1	w_2	w_3	w_4
0.1	0.10	16.031	38.673	0	0	0	1	0.354	0.226	0.146	0.274
0.2	0.05	23.335	63.612	0.039	0.086	0.166	0.708	0.291	0.284	0.209	0.216
0.2	0.10	12.117	33.502	0	0	0	1	0.308	0.279	0.192	0.221
0.2	0.20	6.060	16.756	0	0	0	1	0.309	0.279	0.191	0.221
0.4	0.10	9.163	29.157	0	0	0	1	0.264	0.315	0.236	0.185

θ_3	θ_4	t_2^*	t_3^*	e_3 -optimal				e_4 -optimal			
				w_1	w_2	w_3	w_4	w_1	w_2	w_3	w_4
0.1	0.10	16.031	38.673	0.244	0.398	0.256	0.102	0.140	0.284	0.360	0.216
0.2	0.05	23.335	63.612	0.239	0.399	0.261	0.101	0.137	0.286	0.363	0.214
0.2	0.10	12.117	33.502	0.232	0.391	0.268	0.109	0.127	0.270	0.373	0.230
0.2	0.20	6.060	16.756	0.232	0.391	0.268	0.109	0.127	0.270	0.373	0.230
0.4	0.10	9.163	29.157	0.217	0.378	0.283	0.122	0.114	0.255	0.386	0.245

In all cases, $t_1^*=0, t_4^*=T=120$

Table 2

Locally D -optimal designs $\{t_1^{*D}, t_2^{*D}, t_3^{*D}, t_4^{*D}; w_1, w_2, w_3, w_4\}$ for the Emax/mono-compartment model defined in (5) and their e_j -efficiencies, $i = 1, 2, 3, 4$. In all cases, $t_1^{*D} = 0, t_4^{*D} = T = 120$ and $w_i = 1/4, i = 1, 2, 3, 4$

θ_i	θ_4	t_2^{*D}	t_3^{*D}	eff ₁	eff ₂	eff ₃	eff ₄
0.1	0.10	17.645	36.667	0.252	0.917	0.799	0.842
0.2	0.05	25.860	60.310	0.471	0.957	0.802	0.844
0.2	0.10	13.479	31.616	0.251	0.951	0.810	0.836
0.2	0.20	6.741	15.812	0.250	0.951	0.810	0.836
0.4	0.10	10.278	27.386	0.251	0.932	0.824	0.827

Table 3

Locally standardized maximin optimal designs $\{t_1^*, t_2^*, t_3^*, t_4^*, w_1, w_2, w_3, w_4\}$ with respect to the criterion (2) for the Emax/mono-compartment model defined in (5). In all cases, $t_1^*=0$ and $t_4^*=T$

Criterion (2) with $J = \{1, 2, 3, 4\}$											
θ_3	θ_4	t_2^*	t_3^*	w_1	w_2	w_3	w_4	eff ₁	eff ₂	eff ₃	eff ₄
0.1	0.10	17.001	42.077	0.108	0.183	0.150	0.559	0.564	0.611	0.564	0.607
0.2	0.05	24.552	65.193	0.139	0.242	0.198	0.421	0.715	0.804	0.715	0.793
0.2	0.10	12.916	36.811	0.104	0.179	0.154	0.564	0.567	0.627	0.567	0.610
0.2	0.20	6.462	18.430	0.103	0.178	0.154	0.565	0.565	0.625	0.565	0.609
0.4	0.10	9.797	32.326	0.097	0.173	0.160	0.570	0.572	0.620	0.572	0.616

Criterion (5) with $J = \{2, 3, 4\}$											
θ_3	θ_4	t_2^*	t_3^*	w_1	w_2	w_3	w_4	eff ₂	eff ₃	eff ₄	
0.1	0.10	16.025	38.701	0.260	0.282	0.247	0.212	0.904	0.904	0.904	
0.2	0.05	23.491	63.381	0.215	0.319	0.287	0.179	0.944	0.944	0.944	
0.2	0.10	12.167	33.275	0.220	0.298	0.287	0.195	0.933	0.933	0.933	
0.2	0.20	6.085	16.643	0.220	0.298	0.287	0.195	0.933	0.933	0.933	
0.4	0.10	9.261	28.892	0.183	0.303	0.320	0.194	0.945	0.945	0.945	

Table 4

Robust standardized maximin optimal designs for the Emax/mono-compartment model defined in (5)

5-Point robust design for criterion (4) with $J = \{1, 2, 3, 4\}$					
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	
0	8.355	20.986	51.299	120	
w_1	w_2	w_3	w_4	w_5	min eff
0.164	0.221	0.254	0.114	0.247	0.265

6-Point robust design for criterion (4) with $J = \{1, 2, 3, 4\}$					
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*
0	7.178	16.665	30.966	60.097	120
w_1	w_2	w_3	w_4	w_5	w_6
0.121	0.139	0.157	0.125	0.108	0.349
					0.386

5-Point robust design for criterion (4) with $J = \{2, 3, 4\}$					
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	
0	8.622	20.521	50.073	120	
w_1	w_2	w_3	w_4	w_5	min eff
0.176	0.252	0.308	0.140	0.124	0.280

6-Point robust design for criterion (4) with $J = \{2, 3, 4\}$					
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*
0	7.041	16.702	30.803	57.507	120
w_1	w_2	w_3	w_4	w_5	w_6
0.171	0.166	0.198	0.166	0.176	0.123
					0.472

The set Ω in the criterion (4) is given by $\Omega = \{\theta: 0.1 \leq \theta_3 \leq 0.4, 0.05 \leq \theta_4 \leq 0.2\}$. The extreme right column shows the minimal efficiency calculated over the set Ω and the index set J containing parameters of interest

Locally e_j -optimal designs $\{t_1^*, t_2^*, t_3^*, t_4^*, t_5^*; w_1, w_2, w_3, w_4, w_5\}$ for the Emax/effect-compartment model defined in (7), $j = 2, 3, 4, 5$. In all cases, $t_1^* = 0$

Table 5

θ_3	θ_4	θ_5	e_2 -optimal					w_1	w_2	w_3	w_4	w_5
			t_2^*	t_3^*	t_4^*	t_5^*						
0.1	0.10	0.5	0.025	2.032	17.512	40.465	0	0.364	0.432	0.136	0.068	0.068
0.2	0.05	0.5	0.073	2.436	23.994	68.486	0	0.309	0.399	0.191	0.101	0.101
0.2	0.10	0.3	0.155	3.641	17.801	39.117	0	0.339	0.404	0.161	0.096	0.096
0.2	0.10	0.5	0.085	2.331	14.223	35.800	0	0.325	0.407	0.175	0.093	0.093
0.2	0.10	0.9	0.042	1.347	12.160	34.386	0	0.311	0.401	0.189	0.099	0.099
0.2	0.20	0.5	0.096	2.108	9.706	20.553	0	0.344	0.402	0.156	0.097	0.097
0.4	0.10	0.5	0.219	2.717	12.415	33.462	0	0.297	0.366	0.202	0.134	0.134

θ_3	θ_4	θ_5	e_3 -optimal					w_1	w_2	w_3	w_4	w_5
			t_2^*	t_3^*	t_4^*	t_5^*						
0.1	0.10	0.5	0.073	2.302	18.210	42.029	0	0.152	0.277	0.348	0.223	0.223
0.2	0.05	0.5	0.131	2.694	25.382	71.467	0	0.161	0.278	0.339	0.221	0.221
0.2	0.10	0.3	0.234	3.898	18.284	40.642	0	0.205	0.248	0.295	0.252	0.252
0.2	0.10	0.5	0.149	2.583	14.947	37.915	0	0.185	0.269	0.315	0.231	0.231
0.2	0.10	0.9	0.075	1.488	12.883	35.993	0	0.164	0.279	0.336	0.221	0.221
0.2	0.20	0.5	0.128	2.205	9.862	21.037	0	0.210	0.238	0.290	0.262	0.262
0.4	0.10	0.5	0.255	2.816	12.742	34.733	0	0.219	0.259	0.281	0.241	0.241

θ_3	θ_4	θ_5	e_4 -optimal					w_1	w_2	w_3	w_4	w_5
			t_2^*	t_3^*	t_4^*	t_5^*						
0.1	0.10	0.5	0.013	1.962	17.409	40.303	0	0.231	0.162	0.268	0.338	0.338
0.2	0.05	0.5	0.032	2.272	23.304	67.423	0	0.250	0.161	0.250	0.339	0.339
0.2	0.10	0.3	0.035	3.315	17.383	38.173	0	0.261	0.131	0.239	0.369	0.369
0.2	0.10	0.5	0.031	2.152	13.867	35.059	0	0.255	0.150	0.245	0.350	0.350
0.2	0.10	0.9	0.018	1.252	11.806	33.815	0	0.250	0.161	0.250	0.339	0.339
0.2	0.20	0.5	0.016	1.878	9.470	20.017	0	0.261	0.126	0.238	0.374	0.374

θ_3			θ_4	θ_5	e_4 -optimal					w_1	w_2	w_3	w_4	w_5
					t_2^*	t_3^*	t_4^*	t_5^*						
0.4	0.10	0.5			0.059	2.319	11.536	30.803	0	0.279	0.137	0.221	0.363	

θ_3			θ_4	θ_5	e_5 -optimal					w_1	w_2	w_3	w_4	w_5
					t_3^*	t_4^*	t_5^*							
0.1	0.10	0.5			0.989	16.327	39.611	0.105	0	0.309	0.395	0.191		
0.2	0.05	0.5			1.589	21.174	65.989	0.103	0	0.318	0.397	0.182		
0.2	0.10	0.3			2.025	16.528	37.522	0.140	0	0.257	0.360	0.243		
0.2	0.10	0.5			1.449	13.019	34.306	0.114	0	0.296	0.386	0.204		
0.2	0.10	0.9			0.883	10.766	33.101	0.103	0	0.318	0.397	0.182		
0.2	0.20	0.5			1.129	9.042	19.731	0.154	0	0.241	0.346	0.259		
0.4	0.10	0.5			1.897	11.013	30.156	0.130	0	0.271	0.370	0.229		

Table 6

Locally D -optimal designs $\{t_1^{*D}, t_2^{*D}, t_3^{*D}, t_4^{*D}, t_5^{*D}; w_1, w_2, w_3, w_4, w_5\}$ for the Emax/effect-compartment model defined in (7) and their e_j -efficiencies, $j = 1, 2, 3, 4, 5$. In all cases, $t_5^{*D} = T = 120$ and $w_i = 1/5, i = 1, 2, 3, 4, 5$

θ_3	θ_4	θ_5	t_1^{*D}	t_2^{*D}	t_3^{*D}	t_4^{*D}	eff_1	eff_2	eff_3	eff_4	eff_5
0.1	0.10	0.5	0.165	2.812	18.655	37.883	0.201	0.613	0.635	0.701	0.616
0.2	0.05	0.5	0.293	3.347	25.578	62.389	0.200	0.638	0.619	0.691	0.576
0.2	0.10	0.3	0.448	4.464	18.368	36.119	0.200	0.617	0.673	0.689	0.637
0.2	0.10	0.5	0.280	2.947	14.694	32.650	0.200	0.622	0.643	0.704	0.605
0.2	0.10	0.9	0.162	1.819	12.875	31.270	0.200	0.635	0.621	0.695	0.578
0.2	0.20	0.5	0.264	2.560	10.020	19.031	0.200	0.616	0.681	0.678	0.645
0.4	0.10	0.5	0.428	3.083	12.105	28.503	0.200	0.615	0.648	0.696	0.611

Table 7

Locally standardized maximin optimal designs $\{t_1^*, t_2^*, t_3^*, t_4^*, t_5^*; w_1, w_2, w_3, w_4, w_5\}$ with respect to the criterion (2) for the Emax/effect-compartment model defined in (7)

Criterion (2) with $J = \{1, 2, 3, 4, 5\}$																
θ_3	θ_4	θ_5	t_2^*	t_3^*	t_4^*	t_5^*	w_1	w_2	w_3	w_4	w_5	eff ₁	eff ₂	eff ₃	eff ₄	eff ₅
0.1	0.10	0.5	0.133	2.28	18.12	43.6	0.505	0.065	0.150	0.166	0.114	0.505	0.505	0.505	0.531	0.505
0.2	0.05	0.5	0.224	2.53	23.96	73.2	0.497	0.072	0.160	0.166	0.105	0.498	0.498	0.498	0.512	0.498
0.2	0.10	0.3	0.336	4.03	17.46	40.6	0.486	0.094	0.171	0.140	0.110	0.487	0.487	0.501	0.498	0.487
0.2	0.10	0.5	0.215	2.49	13.88	37.6	0.490	0.083	0.171	0.156	0.100	0.490	0.490	0.493	0.493	0.490
0.2	0.10	0.9	0.131	1.46	12.03	36.8	0.496	0.070	0.162	0.170	0.102	0.496	0.496	0.496	0.502	0.496
0.2	0.20	0.5	0.190	2.36	9.60	21.2	0.485	0.100	0.168	0.133	0.115	0.486	0.486	0.506	0.501	0.486
0.4	0.10	0.5	0.310	2.77	11.91	33.5	0.478	0.104	0.162	0.147	0.108	0.478	0.478	0.509	0.489	0.478

Criterion (2) with $J = \{2, 3, 4, 5\}$																
θ_3	θ_4	θ_5	t_2^*	t_3^*	t_4^*	t_5^*	w_1	w_2	w_3	w_4	w_5	eff ₂	eff ₃	eff ₄	eff ₅	
0.1	0.10	0.5	0.094	1.92	16.17	39.9	0.149	0.124	0.315	0.267	0.145	0.754	0.760	0.754	0.754	
0.2	0.05	0.5	0.175	2.28	21.34	65.7	0.105	0.142	0.304	0.288	0.161	0.773	0.773	0.773	0.773	
0.2	0.10	0.3	0.304	3.60	16.57	37.3	0.121	0.161	0.283	0.256	0.180	0.727	0.791	0.727	0.727	
0.2	0.10	0.5	0.174	2.22	13.02	34.0	0.106	0.153	0.301	0.276	0.164	0.752	0.764	0.752	0.752	
0.2	0.10	0.9	0.096	1.26	10.96	32.8	0.104	0.142	0.306	0.288	0.160	0.771	0.771	0.771	0.771	
0.2	0.20	0.5	0.183	2.11	9.08	19.6	0.129	0.162	0.277	0.244	0.187	0.718	0.804	0.718	0.718	
0.4	0.10	0.5	0.306	2.59	11.21	30.0	0.103	0.171	0.273	0.266	0.186	0.733	0.776	0.733	0.733	

For all the cases, $t_1^*=0$

Table 8

Robust standardized maximin optimal designs for the Emax/effect-compartment-model defined in (7)

6-Point robust design for criterion (4) with $J = \{1, 2, 3, 4, 5\}$						
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*	
0	0.372	2.663	9.700	21.765	52.112	
w_1	w_2	w_3	w_4	w_5	w_6	min eff
0.206	0.080	0.178	0.159	0.253	0.125	0.206
7-Point robust design for criterion (4) with $J = \{1, 2, 3, 4, 5\}$						
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*	t_7^*
0	0.210	1.863	5.619	13.690	26.264	55.369
w_1	w_2	w_3	w_4	w_5	w_6	w_7
0.262	0.098	0.126	0.110	0.107	0.173	0.125
						0.262
6-Point robust design for criterion (4) with $J = \{2, 3, 4, 5\}$						
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*	
0	0.308	2.557	9.581	21.245	51.054	
w_1	w_2	w_3	w_4	w_5	w_6	min eff
0.086	0.104	0.191	0.187	0.267	0.165	0.218
7-Point robust design for criterion (4) with $J = \{2, 3, 4, 5\}$						
t_1^*	t_2^*	t_3^*	t_4^*	t_5^*	t_6^*	t_7^*
0	0.181	1.809	5.904	13.990	26.894	53.788
w_1	w_2	w_3	w_4	w_5	w_6	w_7
0.106	0.115	0.145	0.129	0.118	0.212	0.175
						0.296

The set Ω in the criterion (4) is given by $\Omega = \{\theta : 0.1 \leq \theta_3 \leq 0.4, 0.05 \leq \theta_4 \leq 0.2, 0.3 \leq \theta_5 \leq 0.9\}$. The extreme right column shows the minimal efficiency calculated over the set of Ω and the index set J containing parameters of interest