Optimal dose-finding for efficacy–safety models

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Abstract
Dose-finding is an important part of the clinical development of a new drug. The purpose of dose-finding studies is to determine a suitable dose for future development based on both efficacy and safety. Optimal experimental designs have already been used to determine the design of this kind of studies, however, often that design is focused on efficacy only. We consider an efficacy–safety model, which is a simplified version of the bivariate Emax model. We use here the clinical utility index concept, which provides the desirable balance between efficacy and safety. By maximizing the utility of the patients, we get the estimated dose. This desire leads us to locally c-optimal designs. An algebraic solution for c-optimal designs is determined for arbitrary c vectors using a multivariate version of Elfving’s method. The solution shows that the expected therapeutic index of the drug is a key quantity determining both the number of doses, the doses itself, and their weights in the optimal design. A sequential design is proposed to solve the complication of parameter dependency, and it is illustrated in a simulation study.

KEYWORDS
bivariate model, dose-finding, Elfving’s method, optimal design, sequential design

1 | INTRODUCTION

During the development process for a new drug, the decision for a good dose to treat patients needs to be made. Usually, this so-called dose-finding is done in Phase II of the development process which is divided into four phases. Bornkamp (2017) gives an overview of dose-finding with background, common objectives, and statistical models appropriate for dose-finding. The book from Ting (2006) introduces several statistical topics occurring in dose-finding. The dose identified in the dose-finding part of development is then usually used in the following Drug Development Phase III in large registration trials. In the best case when these trials are successful, the dose can then be the recommended dose for patients aftermarket authorization. Therefore, dose-finding is of key importance during drug development. Burman et al. (2010) identified areas where the way to conduct dose-finding has the potential for improvement.

Optimal experimental design theory (Atkinson et al., 2007; Fedorov & Leonov, 2015) has been identified as method to improve dose-finding designs; see, for example, Zhu and Wong (2000); Miller et al. (2007); Dette et al. (2008); Burman et al. (2010); Pinheiro and Bornkamp (2017). A recent review was written by Sverdlov et al. (2020). The majority of methodological development on optimal designs focuses on univariate outcomes like a single efficacy observation. This
focus on a univariate outcome has been seen as a limitation in the methodology since almost all clinical trials, in reality, are concerned with both efficacy and safety. An important purpose of dose-finding studies is to estimate the dose that would provide significant effects and at the same time keep side effects low. To consider both efficacy and safety, we need to work on optimal designs for bivariate or multivariate observations. Optimal dose-finding designs have been investigated when efficacy and safety are binary variables; see Section 6.4 in Fedorov and Leonov (2015) and the references cited there. Investigations for continuous bivariate outcomes are rarer: Padmanabhan et al. (2010) considered D-optimal designs for efficacy and toxicity endpoints, which were penalized to take also individual ethics of the patients in the study into account. Magnusdottir (2013) optimized designs for bivariate Emax models using the \( c \)-optimality criterion. Schorning et al. (2017) derived D-optimal designs for bivariate polynomial and Emax models, and Magnusdottir (2016) computed D-optimal designs for multivariate Emax models numerically for a diabetes dose–response study.

The choice of the optimality criterion should be based on the exact objective of the study. In the case of a bivariate efficacy–safety model, we use the Clinical Utility Index (CUI) to eliminate the two characteristics, efficacy and safety, to a single metric. Ouellet (2010) and Carrothers et al. (2011) modeled the CUI function as a weighted sum of effects and side effects for a dose. Freise et al. (2017) and Zhu et al. (2019) applied the approach for benefit–risk analyses for dose selection in cancer trials. Luu and Boni (2016) applied the approach both for dose and dose regimen optimization. Based on a review of U.S. Food and Drug Administration (FDA) decisions about multiple myeloma, Raju et al. (2018) concluded that FDA approval decision outcomes were consistent with their benefit–risk framework; their framework has similarities to the CUI approach. As we will discuss in Section 2.3, the \( c \)-optimal design is suitable when the study focuses on estimating the parameters by maximizing patients’ utility. Specifically, a locally \( c \)-optimal design is conducted to overcome the problem of nonlinear models, where the Fisher information matrix depends on the unknown parameters. So the optimal design is calculated by using prior values for them.

We derive here \( c \)-optimal designs based on the geometric characterization by Elfving (1952); see also, for example, Pukelsheim (1981, 2006); Dette (1993); Dette and Studden (1993), using an extension to multivariate models described by Dette and Holland-Letz (2009), Sagnol (2011), and Liu et al. (2013). With this method, we are able to obtain insights on the structure of optimal designs for the bivariate efficacy–safety model. The geometry of the multivariate Elfving set reveals the \( c \)-optimal design points and weights, for arbitrary \( c \)-vectors.

In contrast to Magnusdottir (2013), we use here the multivariate Elfving approach, and, moreover, we use a log-transformed dose scale in order to get symmetrical design points. With these approaches, we are able to derive explicit optimal design solutions for the simple Emax efficacy–safety model without restrictions on the \( c \)-vector, the correlation between the outcomes, or the assumed parameters for the local optimality.

In order to overcome the complication of unknown true model parameters, a sequential design procedure is applied. The first step in the sequential construction is to find a locally optimal design based on an assumption about the parameters. The parameters are reestimated by using that design and then lead to another locally optimal design which gives us new estimates. The process is repeated many times, and we will see that the design gradually moves to the optimal one. For clinical dose-finding trials, it has been often not possible to do many reanalyses of parameters during the trial and therefore adaptive two-stage designs have been used where only one parameter estimation and optimal design calculation is done during the trial. Investigations of optimal designs in adaptive two-stage dose-finding trials when considering efficacy only have been done by Miller et al. (2007), who draw the conclusion that the two-stage design does not provide a large efficiency gain compared to the one-stage design in their situation. Mielke and Dragalin (2017) examine the adaptive two-stage design for the estimation of the dose, and they show that the two-stage provides the potential for better treatment comparison. Donohue et al. (2010) and Miller et al. (2014) describe two-stage case studies for the treatment of chronic obstructive pulmonary disease and osteoarthritis, respectively. Dragalin et al. (2010) point out advantages from several parameter reestimation during a dose-finding trial, and Krams et al. (2003) present a case study where sequential reestimation was used. Since electronic data capture becomes more and more standard, continuous monitoring of trial results becomes feasible (Friede & Miller, 2012) and fully sequential dose-finding trials are a possibility. Fackle-Fornius (2008) used a sequential design method for binary data to maximize the probability of response.

2 | METHODS

2.1 | The model

A suggestion of Magnusdottir (2013) was to expand the traditional Emax model to two dimensions, one for the efficacy variable \( Y_1 \) and one for the safety \( Y_2 \). So she constructed an optimal design by studying both efficacy and safety
simultaneously. The simple bivariate efficacy–safety model is the following:

\[ Y_1 = \frac{x}{x + ED_{50}} + \varepsilon_1, \quad Y_2 = \frac{x}{x + SD_{50}} + \varepsilon_2, \]

where \((\varepsilon_1, \varepsilon_2) \sim \mathcal{N}(0, \Sigma), x \in \mathcal{X}\) represents the dose of the drug from some design space \(\mathcal{X}\), \(ED_{50}\) represents the dose that gives 50% of the maximal effect and \(SD_{50}\) represents the dose that gives 50% of the maximal side effect.

The idea in this article is to consider a log-transformed dose scale for both efficacy and safety simultaneously, which leads to useful shift and symmetry properties and will make it later possible to compute designs explicitly. The simple log-transformed dose scale efficacy–safety model is defined as

\[ Y_1 = \frac{1}{1 + \exp\{-(y - a_E)\}} + \varepsilon_1, \quad Y_2 = \frac{1}{1 + \exp\{-(y - a_S)\}} + \varepsilon_2, \quad (1) \]

where \((\varepsilon_1, \varepsilon_2) \sim \mathcal{N}(0, \Sigma), y = \log(x)\) represents the dose of the drug in the logarithm scale, \(a_E = \log(ED_{50})\) is the logarithm of the dose that gives the 50% of the maximal effect, and \(a_S = \log(SD_{50})\) represents the logarithm of the dose that gives 50% of the maximal side effect. We can write the simple bivariate efficacy–safety model as \(Y = h(y) + \varepsilon\) with \(Y = (Y_1, Y_2)^T, \varepsilon = (\varepsilon_1, \varepsilon_2)^T\) and \(h(y) = (h_1(y), h_2(y))^T = ([1 + \exp\{-(y - a_E)\}]^{-1}, [1 + \exp\{-(y - a_S)\}]^{-1})^T\). The efficacy and safety model have the same shape for all parameters, and the safety model is the shifted efficacy model: \(h_1(y) = h_2(y - a_E + a_S)\).

In this article, we generally consider an unrestricted design space for the doses, \(\mathcal{X} = [0, \infty)\). On the log-transformed scale, it corresponds to the unrestricted interval of real numbers \(\mathcal{Y} = (-\infty, +\infty)\), where \(-\infty\) is corresponding to placebo. We will discuss later in Example 3.4 the case when an upper bound \(U\) is given for the allowed log-doses, \(\mathcal{Y} = [-\infty, U]\) and present a result for this restricted design space. Further, we will show results about the number of design points needed for the optimal design which are valid for arbitrary design spaces \(\mathcal{Y}\).

Example 2.1. Tooth extraction studies (see, e.g., Quiding et al., 2013) can be used as pain models. This pain model allows to investigate the effect of a pain-reducing drug early in Phase II drug development. The study makes it also possible to collect safety information in a patient population. In the study of Quiding et al. (2013), increased body temperature was a safety issue which had been identified in preclinical and Phase I studies and was therefore prospectively analyzed. We assume here that a tooth extraction study should be conducted for a new pain drug. Further, we assume that a continuous efficacy endpoint measuring pain reduction and a continuous safety endpoint can be described by the efficacy–safety-model (1) for log-dose \(y\). The research team has the prior assumption that the \(ED_{50}\) is attained for a dosage of 1 mg and the \(SD_{50}\) for 10 mg (\(a_E = 0, a_S = 2.30\) on the log-scale).

2.2 The clinical utility index

In pharmaceutical drug development, an important goal is to find the dose of a potential drug that will give the most positive effects and the least side effects. As Carrothers et al. (2011) mentioned, the CUI is one of the multiattribute utility analysis models that can be used to narrow down multiple characteristics to a single number. In dose-finding studies, CUI has been introduced to find the desired balance between safety and efficacy. The efficacy and safety are only two characteristics out of many that should be taken into consideration when we consider the dose of a drug.

In Ouellet (2010), the CUI function is defined as the algebraic sum of \(k_i\) times \(U_i\) as \(CUI = \sum_{i=1}^{n} k_i U_i\), where \(k_i\) represents the weight and \(U_i\) is the utility function for each characteristic. In drug research, the CUI function for a given dose of a drug and for a particular level of efficacy and safety is a weighted sum of the benefits and risks,

\[ CUI(y) = k_1 h_1(y) - k_2 h_2(y), \]

where \(k_1, k_2 > 0\) represent the weight of efficacy and safety, respectively, and in our case a negative sign is used in the case of safety.

The desirable dose is the one that maximizes the utility index. Note that \(CUI(y)\) has a maximum for some \(y\) if and only if the following two conditions are fulfilled: \(k_1 \exp(a_S) - k_2 \exp(a_E) > 0\) and \(k_2 \exp(a_S) - k_1 \exp(a_E) > 0\). If the first condition is not met, \(CUI(y)\) is increasing for \(y \to -\infty\) (best dose = placebo). If the second condition is not met, \(CUI(y)\) is
increasing for \( y \to \infty \) (dose \( \infty \) would theoretically be best). We assume in the sequel that \( k_1 \exp(a_S) - k_2 \exp(a_E) > 0 \) and \( k_2 \exp(a_S) - k_1 \exp(a_E) > 0 \). For the simple bivariate Emax model, the dose in the log-scale is given by using the following formula:

\[
g(\theta) = \arg \max \{CUI(y) : y \in \mathcal{Y} \} = \log \left\{ \frac{\exp(a_E) - \exp(a_S)}{k_1 \exp(a_E) - k_2 \exp(a_S)} \sqrt{k_1 k_2 \exp(a_E) \exp(a_S) - \exp(a_E) \exp(a_S) (k_1 - k_2)} \right\},
\]

where \( \theta = (a_E, a_S)^T \); see Magnusdottir (2013).

Our aim is to estimate the dose maximizing the CUI in a clinical study. For this, we want now to compute a good study design.

### 2.3 c-Optimal designs for maximizing the CUI

We use standard experimental design notation (see, e.g., Atkinson et al., 2007) to demonstrate the optimal design of the dose-finding study. Let \( \xi \) be a design, determined by \( n \geq 1 \) design points \( y_i \) and weights \( w_i \)

\[
\xi = \begin{pmatrix} y_1 & \cdots & y_n \\
1 & \cdots & w_n \end{pmatrix},
\]

where the sum of the positive \( w_i \) is equal to 1. In our case, \( y_i \) denotes the \( i \)th log-dose of a drug and the \( w_i \) is the proportion of the patients, who receive the \( i \)th log-dose. To ensure that the parameters in our model can be estimated, we exclude the design which has all observations on \( y_1 = -\infty \) (placebo); for all other designs, the model parameters are estimable.

For the design that assigns all observations at one dose \( y \), we use the notation \( \xi_y \). The standardized information matrix \( M \) for the simple log-transformed dose scale efficacy–safety model is

\[
M(\xi_y) = \left( \frac{\partial h}{\partial a_E} \frac{\partial h}{\partial a_S} \right) \Sigma^{-1} \left( \frac{\partial h}{\partial a_E} \frac{\partial h}{\partial a_S} \right)^T
\]

\[
= \frac{1}{1 - \rho^2} \begin{pmatrix}
\frac{1}{\sigma_1^2} \frac{\exp(-y+a_E)^2}{[1+\exp(-y+a_E)]^4} & -\rho \frac{\exp(-y+a_E) \exp(-y+a_S)}{\sigma_1 \sigma_2 [1+\exp(-y+a_E)]^2 [1+\exp(-y+a_S)]^2} \\
-\rho \frac{\exp(-y+a_E) \exp(-y+a_S)}{\sigma_1 \sigma_2 [1+\exp(-y+a_E)]^2 [1+\exp(-y+a_S)]^2} & \frac{1}{\sigma_2^2} \frac{[\exp(-y+a_S)]^2}{[1+\exp(-y+a_S)]^4}
\end{pmatrix}
\]

where

\[
\Sigma = \begin{pmatrix}
\sigma_1^2 & \sigma_1 \sigma_2 \rho \\
\sigma_1 \sigma_2 \rho & \sigma_2^2
\end{pmatrix}
\]

with \( \sigma_1, \sigma_2 > 0, \rho \in (-1, 1) \). The standardized information matrix for the design \( \xi \) is given by

\[
M(\xi) = \sum_{i=1}^{n} w_i M(\xi_y).
\]

Let \( c \) be a vector of known constants. Estimating the linear combination of the parameters \( c^T \theta \) with minimum variance is \( c \)-optimality’s function. In \( c \)-optimality, the criterion function to be maximized is

\[
\{c^T M(\xi)^{-1} c\}^{-1}.
\]

We consider the \( c \)-optimality criterion since the aim of this article is to determine the dose \( g(\theta) \) that maximizes the utility index. Minimizing the variance of the estimator for \( g(\theta) \) can be achieved by a \( c \)-optimal design, where \( c \) is a \( 2 \times 1 \) vector \( c = (\partial g/\partial a_E, \partial g/\partial a_S)^T \); see Magnusdottir (2013).
Note that in general, the c-optimality criterion allows for designs \( \xi \) which lead to noninvertible matrices \( M(\xi) \) as long as \( c^T \Theta \) is estimable. For this, a generalized inverse \( M(\xi)^{-} \) can be used instead of \( M(\xi)^{-1} \) in the criterion (2). In our case, however, one can show that \( M(\xi) \) is invertible for all designs \( \xi \); see the Supporting Information for more details.

If \( k_2 = mk_1 \) with \( m > 0 \), then the \( c \)-vector depends only on the variable \( SD_{50}/ED_{50} \) and is

\[
c = \left( \sqrt{m + 2(m - 1)/SD_{50}/ED_{50}}, \sqrt{m} \right)^T.
\]

In the important case when efficiency and safety have the same weight in the CUI, \( m = 1 \), we have \( c = (1, 1)^T \). If \( m > 1 \) (more weight on safety), \( c = (c_1, \sqrt{m})^T \) with \( c_1 > \sqrt{m} \). If \( a_S - a_E \) is large, the \( c \)-vector is approximately into the same direction as \( (1, 1)^T \) for any \( m \).

**Example 2.2 (Example 2.1 continued).** For our tooth extraction study, the research team has determined that a CUI with double weight on safety, \( m = 2 \), should be used. Based on the assumed \( ED_{50} = 1, SD_{50} = 10 \), we should look for a \( c \)-optimal design with \( c = (\sqrt{2 + 2/\sqrt{10}}, \sqrt{2})^T = (2.047, 1.414)^T \).

### 2.4 Multivariate Elfving

A way to derive the \( c \)-optimal design of a univariate linear model \( f(x)^T \beta + \varepsilon \) is to use a geometric characterization known as the method of Elfving (1952). First, we consider the set \( f(\mathcal{X}) \) in the space \( \mathbb{R}^k \) and the mirrored set \( -f(\mathcal{X}) \). The symmetric convex hull of \( f(\mathcal{X}) \) and \( -f(\mathcal{X}) \) is the Elfving set \( \mathcal{G} = \text{Conv}\{-f(\mathcal{X}) \cup f(\mathcal{X})\} \). We scale the vector \( c \) to touch the boundary of the Elfving set. A design \( \xi \) with doses \( x_1, \ldots, x_n \) and weights \( w_1, \ldots, w_n > 0 \) is \( c \)-optimal if and only if there exist \( e_i \in \{-1, 1\} \) and a positive scalar \( t \) such that the point \( tc \in \mathbb{R}^k \) which touches the boundary of the Elfving set \( \mathcal{G} \) has the form

\[
tc = \sum_{i=1}^{n} w_i f(x_i) e_i.
\]

Dette and Holland-Letz (2009) introduced a multivariate Elfving set to characterize optimal designs in nonlinear heteroscedastic regression models. Later, Sagnol (2011) formulated the multivariate Elfving characterization for the set of multidimensional observations \( f(x) \) in the space \( \mathbb{R}^k \). By taking into consideration, the variance–covariance matrix in the definition of the Elfving set, it becomes

\[
\mathcal{G} = \text{Conv}\{ f(x)^T \Sigma^{-1/2} e, \|e\| = 1 \text{ and } x \in \mathcal{X} \},
\]

where \( \|e\| \) denotes the Euclidean distance or norm, \( \Sigma^{-1/2} \) is the square root of the inverse variance–covariance matrix. It is proved that a design \( \xi \) with doses \( x_1, \ldots, x_n \) and weights \( w_1, \ldots, w_n > 0 \) is \( c \)-optimal if and only if there exist vectors \( e_i \) satisfying \( \|e_i\| = 1 \) and a positive scalar \( t \) such that the point \( tc \in \mathbb{R}^k \) which touches the boundary of the Elfving set \( \mathcal{G} \) defined in (4) has the form

\[
tc = \sum_{i=1}^{n} w_i f(x_i)^T \Sigma^{-1/2} e_i.
\]

In our case, \( f(x) \) is multidimensional and nonlinear. The linearization method is applied to handle the nonlinear efficacy–safety model \( h(y) \). In order to formulate the multivariate Elfving set \( \mathcal{G} \) according to (4), we have to construct the linearized function \( f(y) \) for the bivariate efficacy–safety model, which is

\[
f(y) = \begin{pmatrix}
\frac{\partial h_1}{\partial a_E} & \frac{\partial h_1}{\partial a_S} \\
\frac{\partial h_2}{\partial a_E} & \frac{\partial h_2}{\partial a_S}
\end{pmatrix}
\begin{pmatrix}
0 & f_1(y) \\
0 & f_2(y)
\end{pmatrix},
\]

where \( f_1(y) = \exp(-y + a_E)/(1 + \exp(-y + a_E))^2 \) and \( f_2(y) = \exp(-y + a_S)/(1 + \exp(-y + a_S))^2 \). Assuming that the variance in the efficacy and safety model is both equal to 1, \( \sigma_1^2 = \sigma_2^2 = 1 \), then the square root of inverse
covariance–variance matrix depends only on the values of correlation:

$$\Sigma^{-1/2} = \frac{1}{2(1-\rho)} \begin{pmatrix} \rho_+ & \rho_- \\ \rho_- & \rho_+ \end{pmatrix},$$

where we defined $\rho_- = \sqrt{1-\rho} - \sqrt{1+\rho}$ and $\rho_+ = \sqrt{1-\rho} + \sqrt{1+\rho}$.

Since $h_1(y) = h_2(y - a_E + a_S)$ and therefore $f_1(y) = f_2(y - a_E + a_S)$, our optimal design problem is shift-invariant for our log-transformed model: The information matrix $M(\xi_y)$ in a model with $a_E = 0, a_S = t$ is the same as $M(\xi_{y+a})$ in a model with $a_E = a, a_S = t + a$. Hence, we let without loss of generality $a_E = 0$ ($E_{D50} = 1$). Then we have $f_1(y) = \exp(-y)/[1+\exp(-y)]^2$. Since the Euclidean norm of $\mathbf{e}$ in (4) should be equal to 1, we will assign the vector $\mathbf{e}$ to be $\mathbf{e} = (\sin v, \cos v)^T$ with $v \in [0, 2\pi)$. For fixed $a_S = \log(SD_{50})$ and correlation $\rho$, we have the Elfving set

$$\mathcal{G} = \text{Conv}\left\{G_1, G_2\right\} = \text{Conv}\left\{\begin{pmatrix} \exp(-y) \\ \frac{1}{2(1-\rho)}(\rho_+ \sin v + \rho_- \cos v) \\ \frac{1}{2(1-\rho)}(\rho_- \sin v + \rho_+ \cos v) \end{pmatrix} \middle| y \in \mathcal{Y}, v \in [0, 2\pi) \right\}.$$

To visualize the Elfving set, we start by creating ellipsoids. By setting values to $y$ and $v$ (for any decided correlation $\rho$), we get a value for the $G_1$ and the $G_2$. If we let $v$ to run from 0 to $2\pi$, for the particular value of $y$, we will obtain a set of values for $G_1$ and $G_2$ and by plotting them, we will then have the first ellipsoid. By repeating the same procedure for different values of $y$, we get a collection of ellipsoids. So each ellipsoid corresponds to a different dose. If the set of ellipsoids is not yet convex, we take the convex hull of them to obtain the Elfving set $\mathcal{G}$. We continue by finding the point $\mathbf{c}$ in the plot. We scale the $\mathbf{tc}$-vector until it touches the boundary of the convex hull. The connection between the Elfving set $\mathcal{G}$ and the vector $\mathbf{c}$ constitutes the critical step in solving the problem: the design $\xi$ with design points $x_i$ and weights $w_i$ from (3) are the $\mathbf{c}$-optimal design. The next move is to represent the $\mathbf{tc}$-vector with one or two points from the ellipsoids. These are corresponding to the optimal points, which are on the optimal ellipsoids. If more than one point of the ellipsoids is necessary to represent $\mathbf{c}$, the connection between the optimal points is on the boundary of the convex hull. We point out that the Elfving set $\mathcal{G}$ itself does not depend on the chosen $\mathbf{c}$-vector.

3 | RESULTS FOR LOCALLY $\mathbf{c}$-OPTIMAL DESIGN

3.1 | Number of design points and symmetry property

Before explicitly calculating optimal designs, we identify their structure. Especially, the multivariate Elfving approach gives us information about the number of design points needed when looking for a $\mathbf{c}$-optimal design.

**Theorem 3.1.** For the simple bivariate efficacy–safety model, the following is true:

1. There exists a locally $\mathbf{c}$-optimal design which has at most two design points. This is valid for an arbitrary design space $\mathcal{Y} \subseteq [-\infty, +\infty]$.
2. In the special case $\mathbf{c} = (1, 1)^T$ and design space $\mathcal{Y} = [-\infty, +\infty)$, there is a $\mathbf{c}$-optimal design with at most two support points which is symmetrical around $(a_E + a_S)/2$. This means it can be represented as

$$\xi = \left\{ \begin{array}{l} \frac{a_E + a_S}{2} - \frac{\delta}{2} \frac{a_E + a_S}{2} + \frac{\delta}{2} \\ \frac{a_E + a_S}{2} - \frac{\delta}{2} \frac{a_E + a_S}{2} + \frac{\delta}{2} \end{array} \right\}$$

with $\delta \geq 0$ (in the case $\delta = 0$, we have a one-point design).
Proof. Part 1 follows by geometrical arguments based on the multivariate Elfving method in combination with Carathéodory’s theorem. Part 2 follows due to symmetry arguments for the Elfving set. For more details, see the Supporting Information.

3.2 Special case when utility gives same weight to efficacy and safety

We consider the special case $c = (1, 1)^T$ first, which we obtain when the CUI with $k_1 = k_2$ is applied. In this case, the CUI can be positive, as we have already mentioned, only if $ED_{50} < SD_{50}$. If we would assume that this is not the case, then the development of the drug would not make sense. Therefore, we assume here this relation between these parameters. For the rest of Section 3 with exception of Example 3.4, we assume an unrestricted design space $\mathcal{Y} = [-\infty, \infty]$.

After having outlined the structure of the optimal design, we can now present the $c$-optimal design. The optimal design is dependent on the correlation between efficacy and safety, while it is independent of the variance of the observations. However, we assume that the variances for efficacy and safety are the same. The ratio $TI = SD_{50}/ED_{50}$ used below is a classic definition of the therapeutic index (Muller & Milton, 2012) of the drug under investigation: The larger this index, the better is the opportunity that the drug can be administered in a way giving good effect without major side effects.

Theorem 3.2. We consider the simple bivariate efficacy–safety model with $ED_{50} < SD_{50}$, $\sigma_1 = \sigma_2$, $\rho \in (-1, 1)$ arbitrary, and $c = (1, 1)^T$. Let $TI = SD_{50}/ED_{50}$.

1. If $TI \leq 4/(-\rho + 3 - \sqrt{\rho^2 - 6\rho + 5})^2$, then the one-point design $\xi_y$ with $y = (a_E + a_S)/2 = \log(\sqrt{ED_{50} \cdot SD_{50}})$ is $c$-optimal.

2. If $TI > 4/(-\rho + 3 - \sqrt{\rho^2 - 6\rho + 5})^2$, then the two-point design (6) with

$$
\delta = \log \left\{ \frac{1}{4A} \left( \sqrt{8A^2 - 4AC + B^2 - B} \\
+ \sqrt{2B^2 - 4AC - 8A^2 - 2B\sqrt{8A^2 - 4AC + B^2}} \right) \right\}
$$

(7)

and $A = b + b^5 - 2b^3$, $B = -1 + 5b^2 + 5b^4 - b^6 - 4b^4 - 4b^2$, $C = 2b(-2 + 10b^2 - 2b^4 - \rho + \rho b^4 - 4\rho b^2)$ with $b = \sqrt{ED_{50}/SD_{50}} = \exp\{(a_E - a_S)/2\}$ is $c$-optimal.

The proof can be found in the Supporting Information.

We see that the ratio $TI$ is determining if the optimal design is a one- or two-point design. The result of Theorem 3.2 says, therefore, if we expect the new drug to have a small therapeutic index, a one-point design using the geometric mean of $ED_{50}$ and $SD_{50}$ as dose is optimal; if we expect a large therapeutic index, a design using two doses is the better choice. Heuristically, it is clear that a one-point design cannot be good for a large therapeutic index ($SD_{50}$ and $ED_{50}$ differ much): In this case, a one-point design which is good for estimating the $SD_{50}$ will perform worse for the estimation of $ED_{50}$ and vice versa. Consequently, it is better to take different points which address the parameters.

Numerically for different values of $\rho$, the $\delta$ in the $c$-optimal two-point design (6) is shown in Figure 1 depending on the therapeutic index. The curves start at $TI = 4/(-\rho + 3 - \sqrt{\rho^2 - 6\rho + 5})^2$ since for smaller $TI$, a one-point design is optimal ($\delta = 0$). We focus here in Figure 1 and in some subsequent figures on $\rho \geq 0$ since it is more realistic that efficacy and safety are positively rather than negatively correlated.

Corollary 1 of Magnusdottir (2013) gives the explicit solution for the special case of uncorrelated observations ($\rho = 0$) and $TI \leq (5 + \sqrt{21})/2 \approx 4.791$. Our Theorem 3.2 identifies now the exact cut point between one- and two-point designs, which is $4/(3 - \sqrt{5})^2 = (7 + 3\sqrt{5})/2 \approx 6.854$ for $\rho = 0$, specifies the two-point design for higher $TI$ explicitly, and generalizes the result to arbitrary correlation $\rho$.

The cut point between optimal one- and two-point designs is decreasing with increasing correlation. For $\rho$ close to $-1$, it is $TI = 7 + 2\sqrt{12} \approx 13.928$ while the cut point tends to $TI = 1$ for $\rho$ close to $1$.

In order to better understand the connection between Theorem 3.2 and the Elfving set, we illustrate two cases. In both cases $\rho = 0$, but in the first case we have $TI = 6$ while in the other $TI = 12$, as shown in Figure 2. To construct these two...
FIGURE 1  Optimal $\delta$ for the two-point design depending on $TI = SD_{50}/ED_{50}$ and on $\rho$

FIGURE 2  Elfving set (6) before taking the convex hull (black) for $\rho = 0$; panels for $TI = 6, 12$; green is the direction $c = (1,1)^T$; red points and blue ellipsoids correspond to optimal design points; red line is the convex hull

For large $TI$, the optimal design is a two-point design for any $c$ except for vectors close to $c = (1,0)^T$ and $c = (0,1)^T$ since $tc$ crosses the red boundary and two points on the ellipsoids are necessary to write the crossing point as linear combination (5) of them.
We are now considering correlated outcomes. For $TI = 10$ and $\rho = 0, 0.5, 0.9$, the Elfving set, the direction $t_c$ for $c = (1, 1)^\top$ and the ellipsoids and points corresponding to the optimal design points are shown in Figure 3. Since $TI$ is more than $4/(-\rho + 3 - \sqrt{\rho^2 - 6\rho + 5})^2$, we have a two-point design in all the panels as we showed in the Theorem 3.2. As $\rho$ increases, the distance between the two points of the $c$-optimal design becomes greater. We see that for $\rho = 0.5, 0.9$, the red points are no longer in the quadrant with positive coordinates $G_1$ and $G_2$. This implies that a two-point design is optimal for any $c$-vector coming from a weight $m \geq 1$ between efficacy and safety in the CUI, and the two optimal doses are the same for all $m \geq 1$. Only the weights depend on $m$.

### 3.3 Generalization to arbitrary weighting between efficacy and safety

We discuss now how we can compute $c$-optimal designs for general $c$ based on the results for $c = (1, 1)^\top$ in Theorem 3.2. With this, we can handle CUI with general weighting $k_2 = mk_1, m > 0$. When the $c$-vector is not $c = (1, 1)^\top$ and a two-point design is optimal, we see based on the Elfving sets that the two doses are the same as in the case $c = (1, 1)^\top$, but the weights for the two points are not equal. The weights change according to the distance between the red points corresponding to the optimal dose and the point where the $c$-vector crosses the convex hull (red line). We calculate an optimal design for a $c \neq (1, 1)^\top$ in the following example.

**Example 3.3** (Examples 2.1 and 2.2 continued). For the tooth extraction study design, we consider the case that $k_2 = 2k_1, ED_{50} = 1, SD_{50} = 10$, and $\rho = 0$ implying $c = (2.047, 1.414)^\top$. So the assumption about $ED_{50}$ and $SD_{50}$ means that a reasonably good therapeutic index of 10 is expected. We see in Figure 3 that a two-point design is still optimal even for the new $c$-vector, and we can compute the optimal doses using Theorem 3.2: $\delta$ in (7) is equal to 0.8830. By adding and subtracting the calculated $\delta$ to $(a_E + a_S)/2$, we get the two optimal doses

\[
y_{opt1} = (a_E + a_S)/2 - \delta = \{\log(1) + \log(10)\}/2 - \delta = 0.268
\]

and

\[
y_{opt2} = (a_E + a_S)/2 + \delta = \{\log(1) + \log(10)\}/2 + \delta = 2.034.
\]

These doses correspond to the two blue ellipsoids in Figure 3, if we set $y$ in (6) to these doses and let run $v$ from 0 to $2\pi$.

In order to determine the optimal weight for each dose, we apply the Elfving theory. Due to Formula (5), we obtain the weights when writing the point $t_c$ as a linear combination of points from the blue ellipsoids. We search therefore for the corresponding values of $v$ that will give us the red marked points touching the boundary of the Elfving set. Due to symmetry reasons, these two points lie on a line with slope $-1$ which touches the boundary of the Elfving set (red line in the figure). Therefore, the intercept is the sum of the red points’ coordinates. We look therefore for the $v_1$ and $v_2$, which maximize the sum of the coordinates $(G_1, G_2)$ for $y_{opt1}$ and $y_{opt2}$, respectively. So the values $v_1$ and $v_2$ satisfy
the conditions: \( G_1(y_{opt_1}, v_1) + G_2(y_{opt_1}, v_1) = G_1(y_{opt_2}, v_2) + G_2(y_{opt_2}, v_2) = \max \). With this we obtain numerically the coordinates of point A:

\[
(G_1(y_{opt_2}, v_2), G_2(y_{opt_2}, v_2)) = (G_1(2.034, 4.320), G_2(2.034, 4.320)) = (0.0391, 0.2268)
\]

and of point B:

\[
(G_1(y_{opt_1}, v_1), G_2(y_{opt_1}, v_1)) = (G_1(0.268, 3.534), G_2(0.268, 3.534)) = (0.2268, 0.0391).
\]

Point C has coordinates \( C = (0.157, 0.109) \). Last, we calculate the weight for points A and B based on distance. So the weight for point A is equal to the distance \( ||BC|| \) divided by the distance \( ||AB|| \),

\[
\frac{||BC||}{||AB||} = \frac{\sqrt{(0.2268 - 0.1573)^2 + (0.0391 - 0.1086)^2}}{\sqrt{2(0.0391 - 0.2268)^2}} = 0.3702,
\]

and the weight for point B is equal to the distance \( ||AC|| \) divided by the distance \( ||AB|| \),

\[
\frac{||AC||}{||AB||} = \frac{\sqrt{(0.0391 - 0.1573)^2 + (0.2268 - 0.1086)^2}}{\sqrt{2(0.0391 - 0.2268)^2}} = 0.6298.
\]

The \( c \)-optimal design is

\[
\xi = \left\{ \frac{(ae + as) - \delta (ae + as)}{||AC||/||AB||}, \frac{(ae + as) + \delta}{||BC||/||AB||} \right\} = \left\{ \frac{0.2683}{0.6298}, \frac{2.0342}{0.3702} \right\}.
\]

The points A, B, and C are shown in the left panel of Figure 3. We transform the computed log-doses back and see that the optimal design recommends the use of 1.31 and 7.65 mg in the study. The lower dose 1.31 mg should be used more often for the optimal design, here in about 63% of the cases. In such a situation where more emphasis is on safety, it is usually a good property of the design to be more careful in dosing and to have a higher allocation to the smaller dose.

We see here in the example that the optimal design does not use placebo. The reason for it is that our efficacy and safety models have a known placebo effect which in certain situations is a reasonable assumption. One situation where the placebo effect obviously is 0 is when by design each patient is treated with both placebo and a dose and when placebo-corrected results are then analyzed. However, in situations where a placebo effect is expected which is a priori unknown, models should include a nuisance parameter for the placebo effect. This will usually lead to the need of placebo-treated patients in the optimal design.

**Example 3.4** (Example 3.3 continued). We examine the case that \( k_1 = k_2, ED_{50} = 1, SD_{50} = 10, \rho = 0 \) by taking into consideration an upper dose limit of 5 mg. On the log-scale, we have the dose range \( Y = [-\infty, \log(5)] \). For this restricted case, only ellipsoids for \( y \leq \log(5) \) are included in the Elfving set. The upper left quarter of the Elfving set is shown in Figure 4. As we can see in the figure when we compare it with the left panel of Figure 3, we end up losing some ellipsoids when an upper limit dose is applied. The highest available dose of the restricted design space generates the ellipsoid through point A in the figure, and ellipsoids to the left of it are missing here. The point A is one boundary of the line between A and B from the generated convex hull. As a consequence, the upper dose of a \( c \)-optimal two-point design will be the highest available dose. In our case, the upper dose of the two-point design is the 5 mg and the two-point design is the following:

\[
\xi = \left\{ y_1, \log(5) \right\}.
\]

Since the direction of \( c \) crosses the line A–B of the Elfving set (see Figure 4), a two-point design is still optimal but the weights change when we set an upper dose limit. Based on numerical optimization of the two parameters \( y_1 \) and \( w_1 \), we
FIGURE 4  Elfving set (6) before taking the convex hull (black) for $TI = SD_{50}/ED_{50} = 10$; solid green is the direction $c = (1,1)^\top$; red points A and B and blue ellipsoids through these points correspond to optimal design points (5 and 1.34 mg, respectively)

calculated the $c$-optimal design as follows:

$$\xi = \begin{cases} 0.2951 & 1.6094 \\ 0.3921 & 0.6078 \end{cases}.$$ 

So the nontransformed optimal design that we get has doses 1.34 and 5 mg, as the upper limit that we set. The upper dose 5 mg should be used more often for the optimal design, here in about 60% of the cases. By setting an upper boundary as a restriction to our design and since this limit was lower than the optimal design point that we got at the previous example, we get the upper boundary as one out of two-design points. Also, we see that the other dose changes too, but the major change appears in the weights. Even if $k_1 = k_2$, we do not get equal weights for the two-point design.

### 4  |  SIMULATION STUDY

With the locally optimal design considered so far, we face the problem of parameter dependency. An approach to solve this problem which is widely used in the optimal design area is to apply a sequential design. As discussed in the Introduction, such designs have also been used for clinical dose-finding studies which apply optimal designs.

We start with an initial design. The parameters of the model are then estimated based on the results from that initial design. We can then calculate a new locally optimal design given the current estimate. Next, the information obtained from that new design is used to estimate again the parameters and to find the next locally optimal design, a process that repeats until the maximum number of observations is achieved.

We consider here the case $k_1 = k_2$, which implies that optimal two-point designs have equal weights on both doses. Further, we assume $\varrho = 0$ in the simulations. The sequential approach which we use here can be described by the following steps:

1. Choose $n$ different doses with $n_1$ patients at each dose.
2. Observe the efficacy and safety for all the patients following the initial design. Their data are simulated by generating $\varepsilon_1$ and $\varepsilon_2$ from $N(0, \Sigma)$ and by applying (1).
3. Use the maximum likelihood estimation method and the log-likelihood function as presented in (9) below in order to estimate the model parameters $a_E = \log(ED_{50})$ and $a_S = \log(SD_{50})$ numerically.
4. Based on the new estimates and according to Theorem 3.2, we will obtain either a one-point design or a two-point design. If the ratio $TI = SD_{50}/ED_{50}$ is less than the value that we mentioned in Theorem 3.2 then we will have a one-point design, otherwise a two-point design.
5. The efficacy and the safety are observed for a batch of new patients.
6. $a_E = \log(ED_{50})$ and $a_S = \log(SD_{50})$ are reestimated using the now existing data by using the maximum likelihood estimation method.
7. We repeat Steps 2–6 until we obtain the desirable maximum number of observations.

In our case, the initial design consists of $n = 5$ different doses and $n_i = 10$ patients for each dose, $\omega_i = 0.2$. We have chosen here the initial design

$$\xi_0 = \left\{ \begin{array}{c}
\log(0.1) \log(0.5) \log(5) \log(10) \log(20) \\
0.2 \ 0.2 \ 0.2 \ 0.2 \ 0.2
\end{array} \right\}, \quad (8)$$

or, in words, 10 patients each receive the doses 0.1, 0.5, 5, 10, and 20 mg. After the initial part with $n_{\text{initial}} = 50$ patients, we have the sequential part where 250 patients are included. Since our optimal two-point designs have equal weights, we can include batches of two patients in each iteration. The two patients receive either the same dose or two different doses, such that we have 125 iterations and the total number of patients is $n_{\text{total}} = 300$ in the study. The dose or doses of the two patients in each iteration depend on Theorem 3.2 applied to the current estimates of $a_E$ and $a_S$. When the estimated ratio of $TI = SD_{50}/ED_{50} = \exp(a_S - a_E)$ is less than $4/(3 - \sqrt{5})^2$, then both patients will receive the same dose since a one-point design is optimal, otherwise, they will get two different doses since a two-point design is optimal.

The Maximum Likelihood Estimator (MLE) of $a_E = \log(ED_{50})$ and $a_S = \log(SD_{50})$ is derived from the log-likelihood function (where $N$ is the current number of patients, $Y = (Y_1, \ldots, Y_N)$ are the collected observations and $y_i$ is the log-dose used for patient $i$),

$$\log L(Y_i, a_E, a_S, \Sigma) = -N \log(2\pi) - \frac{N}{2} \log |\Sigma| - \frac{1}{2} \sum_{i=1}^{N} \left( \begin{array}{c}
Y_{1i} - h_1(y_i) \\
Y_{2i} - h_2(y_i)
\end{array} \right)^T \Sigma^{-1} \left( \begin{array}{c}
Y_{1i} - h_1(y_i) \\
Y_{2i} - h_2(y_i)
\end{array} \right)$$

$$= -\frac{1}{2} \sum_{i=1}^{N} \left( \begin{array}{c}
Y_{1i} - [1 + \exp(-(y_i - a_E))]^{-1} \\
Y_{2i} - [1 + \exp(-(y_i - a_S))]^{-1}
\end{array} \right)^T \Sigma^{-1} \left( \begin{array}{c}
Y_{1i} - [1 + \exp(-(y_i - a_E))]^{-1} \\
Y_{2i} - [1 + \exp(-(y_i - a_S))]^{-1}
\end{array} \right)$$

$$= -\frac{1}{2(1 - \rho^2)} \sum_{i=1}^{N} \left[ \frac{1}{\sigma_1^2} \left\{ Y_{1i} - [1 + \exp(-(y_i - a_E))]^{-1} \right\}^2 + \frac{1}{\sigma_2^2} \left\{ Y_{2i} - [1 + \exp(-(y_i - a_S))]^{-1} \right\}^2 - \frac{2\rho}{\sigma_1\sigma_2} \left\{ Y_{1i} - [1 + \exp(-(y_i - a_E))]^{-1} \right\} \left\{ Y_{2i} - [1 + \exp(-(y_i - a_S))]^{-1} \right\} \right]. \quad (9)$$

For Figure 5 (left panel), we used the true parameters $a_E = 0, a_S = \log(10) \approx 2.30, \sigma_1 = \sigma_2 = 1$, and $\rho = 0$ and show the estimates for $a_E$ and $a_S$ after each pair of patients. We see that after the initial design, at patient = 50, the estimates for $a_E$ and $a_S$ are considerably wrong. Then, we apply the locally optimal design sequentially, and the figure shows that the estimated parameters $a_E$ (lower curve, blue) and $a_S$ (upper curve, red) converge to the true values already after a few iterations. The estimated optimal log-dose is close to the true optimal log-dose $g(\theta) = (a_E + a_S)/2 \approx 1.15$ when having 100 patients or more.

Figure 5 (right panel) shows the doses chosen in the sequential design. Whether the optimal design is a one- or a two-point design depends on $TI = \exp(a_S - a_E)$, as we showed in Theorem 3.2 (a one-point design is optimal if and only if the estimated $TI$ is $< \exp(1.925) = 4/(3 - \sqrt{5})^2$). After the first 50 patients, the chosen log-doses vary in both cases between $-3$ and 3 but converge quickly to values around 1. The estimated $TI$ is usually above $4/(3 - \sqrt{5})^2$ leading to choices of both two-point designs. But around patient 250, this estimated $TI$ dropped below the cutoff and a one-point design was optimal.

We repeated simulation of the sequential study 10,000 times and recorded the estimated optimal dose at the end of the trial (true value was $\log(10)/2 \approx 1.15$). As a comparison, we simulated 10,000 times the fixed (nonadaptive) design $\xi_0$ in (8) for 300 patients, that is 60 patients received each of the five doses chosen prior to the study. In two-stage designs, it has
been shown that the size of the initial part is important for the quality of the estimates at the end of the study (Dette et al., 2013). We derive therefore bias and mean squared error (MSE) for the cases \( n_{\text{initial}} = 30, 50, 70, 100, 150, 200, 250 \) (and the fixed design corresponds to \( n_{\text{initial}} = n_{\text{total}} = 300 \)). The bias and the MSE are shown in Table 1. In all cases, the optimal dose was estimated almost without bias. The MSE was better for the sequential optimal designs compared to the fixed design proving the higher precision of the estimate after the sequential design. This shows the value of using a sequential design based on the locally optimal design when the true parameter values of the model are unknown. Too small initial parts have the risk that unreliable estimates might be obtained, and “optimal” doses based on very wrong estimates are chosen. Too large initial parts have the disadvantage that the strength of optimal designs only can be used in a smaller part of the study. The results in Table 1 show that the lowest MSE is achieved for \( n_{\text{initial}} = 50 \); the MSE for \( n_{\text{initial}} = 30 \) and 70 is almost equal and higher \( n_{\text{initial}} \) lead to larger MSE. However, small \( n_{\text{initial}} \) have the disadvantage that extreme results after the initial stage occur with low probability. We discuss this issue and give some more background in the Supporting Information, Section C.

Since estimates are almost unbiased, the standard deviation was almost equal to the root of the MSE. To quantify the uncertainty of the bias and MSE values from the Monte Carlo simulation, we report the 95% bootstrap confidence intervals for them in Table 1.

While we assume normal distribution of the error, the results for bias and MSE are robust against deviation from this assumption. We investigated the case that the error term follows a Gumbel or a negative Gumbel distribution, but the data are analyzed using the MLE (9) based on normal distribution. The results obtained (reported in the Supporting Information, Section D) are almost equal to the results in Table 1.
For the simple univariate model $f(y) = [1 + \exp(-(y - a))]^{-1}$, it is well known that the one-point design using dose $y = a$ is the locally optimal design. In the considered bivariate case, one could, therefore, be tempted to treat half of the patients with dose $a_E$ and half of the patients with dose $a_S$, that is to use the naive design

$$\xi_{\text{naive}} = \left\{ \begin{array}{c}
\log(ED_{50})
\log(SD_{50})
\end{array} \right\}.
$$

Since patients treated with dose $a_E$ give also information on $a_S$ and vice versa, this is not an optimal strategy. We calculate here the relative $c$-efficiency of the naive design versus the locally $c$-optimal design $\xi^*$ specified in Theorem 3.2. This is

$$\{c^T M(\xi_{\text{naive}})^{-1} c\}^{-1}/\{c^T M(\xi^*)^{-1} c\}^{-1}.$$  

The efficiency depends on the therapeutic index $TI = SD_{50}/ED_{50}$, on $\rho$ and on $c$. If $c = (1,1)^T$ and $\rho$ is not large, the performance of the naive design is quite good with efficiencies $> 0.89$ for $\rho = 0$ or $\rho = 0.5$; in many of these cases, the naive design is almost as good as the optimal design. The efficiency can be smaller for higher $\rho$. (See the Supporting Information, Section B, for a graph of efficiency versus $TI$ for $\rho \in \{0,0.5,0.9\}, c = (1,1)^T$.) When $c \neq (1,1)^T$, the optimal design can have two different weights in contrast to the naive design. This can lead to smaller efficiencies for the naive design.

## 5 MODELS WITH MORE PARAMETERS

The focus of this article is the simple bivariate efficacy–safety model (1). In this section, we will show results about the number of design points for efficacy–safety models with more parameters. For one model, we can generalize the proof of Theorem 3.1 (Part 1). For another model, a result of Schorning et al. (2017) gives a sharper bound for the number of design points. For both considered models, $x$ represents the dose of the drug belonging to some design space $X \subseteq [0, \infty)$; we do not log-transform the dose here.

The bivariate Michaelis–Menten efficacy–safety model is the following:

$$Y_1 = E_{\max} \frac{x}{x + ED_{50}} + \varepsilon_1, \quad Y_2 = S_{\max} \frac{x}{x + SD_{50}} + \varepsilon_2,$$

where $(\varepsilon_1, \varepsilon_2) \sim \mathcal{N}(0, \Sigma)$, $ED_{50}$ represents the dose that gives 50% of the maximal effect, $SD_{50}$ represents the dose that gives 50% of the maximal side effect, $E_{\max}$ is the maximum effect that can be achieved while $S_{\max}$ is the maximum side effect. Schorning et al. (2017) derived D-optimal designs for the bivariate Michaelis–Menten efficacy–safety model.

The bivariate Emax–Smax efficacy–safety model is the following:

$$Y_1 = E_0 + E_{\max} \frac{x}{x + ED_{50}} + \varepsilon_1, \quad Y_2 = S_0 + S_{\max} \frac{x}{x + SD_{50}} + \varepsilon_2,$$

where $(\varepsilon_1, \varepsilon_2) \sim \mathcal{N}(0, \Sigma)$, $ED_{50}$ represents the dose that gives 50% of the maximal effect, $SD_{50}$ represents the dose that gives 50% of the maximal side effect, $E_{\max}$ is the maximum effect that can be achieved while $S_{\max}$ is the maximum side effect, and $E_0, S_0$ are the placebo effect and side effect, respectively.

The results in Theorem 5.1 are of importance when locally $c$-optimal designs have to be determined with a numerical algorithm.

**Theorem 5.1.** For any design space $X \subseteq [0, \infty)$, we have the following results about the optimal design’s number of doses:

1. For the bivariate Michaelis–Menten efficacy–safety model (10), there exists a locally $c$-optimal design which has at most four design points.
2. For the bivariate Emax–Smax efficacy–safety model (11), there exists a locally $c$-optimal design which has at most five design points.

**Proof.** Part 1 can be shown with similar arguments as in the proof of Theorem 3.1 (see Supporting Information). Part 2 follows from a result about admissible designs of Schorning et al. (2017) and the Supporting Information of that article.
6 CONCLUSIONS AND DISCUSSION

A naive strategy in bivariate efficacy–safety situations would be to use half of the patients for the optimal efficacy design and half of them for the optimal safety design. Our results show that this is not an optimal strategy, and other designs can be more efficient. Hence, we demonstrated for the models used that it is important to determine the optimal design based on a bivariate model if both efficacy and safety are important endpoints.

The locally c-optimal designs calculated in Section 3 depend on the true, unknown parameter values. As we showed in Section 4, they can be used within a sequential design based on the current parameter estimate. In some situations, however, it is not possible to conduct a clinical trial with a continuous analysis of results. Especially if the patients in the trial have a long follow-up time until their efficacy and safety endpoints can be observed, it can be difficult in some cases to conduct sequential designs. In such cases, Bayesian optimal designs or minimax optimal designs could be used if there is some quantified prior understanding about possible parameter values or ranges. For example, Fackle-Fornius et al. (2015) have computed minimax designs for a single efficacy outcome. A generalization of our work to Bayesian or minimax designs to bivariate efficacy–safety models is a topic for future research. In the motivating example of a tooth-extraction study, the follow-up time is only some hours and it is, therefore, suitable to be analyzed sequentially.

For the usefulness of an optimal design, it is important that the objective of the trial is correctly specified. We have dealt in this article with the objective to identify the dose maximizing the CUI (target dose identification). In some cases, trials can have several objectives. Such cases can be handled in the optimal design methodology. Padmanabhan and Dragalin (2010), for example, consider optimizing both estimation of model parameters and target dose identification (having a univariate outcome). This leads them to augmented and compound designs combining D- and c-optimality.

The use of a multivariate Elfving approach enabled a geometrical construction of locally c-optimal designs for the bivariate efficacy–safety model. The design points can be explicitly computed for arbitrary assumed $ED_{50}$ and $SD_{50}$, for arbitrary correlation $\rho$ between efficacy and safety and for arbitrary $c$. The vector $c$ is determined by the chosen weights in the CUI. Based on the explicit results, we could understand the structure and dependence on parameters of the locally c-optimal design. For example, the expected therapeutic index $SD_{50}/ED_{50}$ is determining the design type. If we expect a high therapeutic index, we should use two doses but focus on one dose if the therapeutic index is smaller.

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CONFLICT OF INTEREST

The authors have declared no conflict of interest.

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