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Research Article

Optimizing Dose-Finding Studies for Drug Combinations Based on Exposure-Response Models

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Abstract. Combinations of pharmacological treatments are increasingly being investigated for potentially higher clinical benefit, especially when the combined drugs are expected to act via synergistic interactions. The clinical development of combination treatments is particularly challenging, particularly during the dose-selection phase, where a vast range of possible combination doses exists. The purpose of this work was to evaluate the added value of using optimal design for guiding the dose allocation in drug combination dose-finding studies as compared with a typical drug-combination trial. Optimizations were performed using local [D(s)-optimality] and global [ED(s)-optimality] optimal designs to maximize the precision of model parameters in a number of potential exposure-response (E-R) surfaces. A compound criterion [D(s)/V-optimality] was used to optimize the precision of model predictions in specific parts of the E-R surfaces. Optimal designs provided unbiased estimates and significantly improved the accuracy of results relative to the typical design. It was possible to improve the efficiency and overall parameter precision up to 7832% and 96.6% respectively. When the compound criterion was used, the probability to accurately identify the optimal dose-combination increased from 71% for the typical design up to 91%. These results indicate that optimal design methodology in tandem with E-R analyses is a beneficial tool that can be used for appropriate dose allocation in dose-finding studies for drug combinations.

KEY WORDS: Dose allocation; Drug combinations; Exposure-response analyses; Optimal design; Response surface.

INTRODUCTION

Increasing understanding of human physiology and pathophysiology has led to the development of specifically targeted drug therapies within therapeutic areas such as oncology, obesity, and diabetes (1–3). The full potential of such treatments, however, has not been realized, as these therapies are typically directed towards a single molecular target, in a physiological system that has evolved to be regulated by a multiplicity of pathways (4). Combinations of targeted treatments can potentially lead to higher clinical benefit, especially when the combined drugs act via synergistic interactions (4,5).

The clinical development of combination treatments is particularly challenging, especially during the dose selection phase, where a vast range of possible combination doses exists (6). Traditionally, drug combination studies for add-on treatments (drug combinations intended for patients previously receiving one of the mono-components and insufficiently responding) and initial combination treatments (drug combinations intended for patients that were previously receiving neither of the mono-components) are conducted based on factorial designs and variation thereof (6,7). While simple in their conception and construction, the choice of the investigated dose levels is often empirical. Quantitative methods, such as model-based drug development (MBDD), have been proposed by regulatory agencies, academia, and pharmaceutical industry as an efficient approach to mitigate the risks of dose selection and improve confidence in decision-making (8,9). As part of MBDD, exposure-response (E-R) analyses associating an exposure metric, such as average concentration in steady state, and a continuous

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response variable measured at a single time point, have become a critical component for supporting dose selection for phase III (10). Nonlinear pharmacodynamic drug interaction models (PDiMs) can be used to describe the E-R relationship of combinatory drug effects (11), which have been shown to be reliable in drug combination dose-finding settings (6).

Further, optimal design methodology (12,13) has been shown to be a powerful tool that can lead to the definition of designs that maximize the obtained information in a clinical study. Optimal design may support a more robust understanding of the underlying biological system by maximizing the overall precision of all (D-optimal design) or part (Ds-optimal design) of the model parameters (14). In addition, designs may be optimized to yield more precise drug effect predictions at specific regions of the E-R relationship (V-optimal design), and thereby potentially maximize the information in an area relevant for dose-selection or further development decisions (15).

In this work, four different E-R relationships were used as general cases, to explore whether using optimal design methodology to help with the allocation of the studied combination doses under a dose-finding trial setting can positively influence the overall collection of information for robustly understanding the underlying clinical pharmacology system. The optimized designs were compared with a typical phase II design (6) in regard to overall parameter accuracy and precision, precision of pre-specified effect level predictions and in regard to their ability to increase confidence in decision-making.

METHODS

Exposure-Response Model

Pharmacodynamic drug interaction models can be used to simultaneously describe the pharmacodynamic interaction profile arising from the combination of two drugs. The model used here allows for differences in the maximum effects of the individual drugs and for the maximum effect of the drug combination:

$$\begin{aligned} E(c_{ss,A}) &= \frac{E_{\max,A}c_{ss,A}^{\gamma_A}}{EC_{50,A}^{\gamma_A}+c_{ss,A}^{\gamma_A}} \\ E(c_{ss,B}) &= \frac{E_{\max,B}c_{ss,B}^{\gamma_B}}{EC_{50,B}^{\gamma_B}+c_{ss,B}^{\gamma_B}} \\ E(c_{ss,A}c_{ss,B}) &= E_0 + E(c_{ss,A}) + E(c_{ss,B}) + \alpha\cdot E(c_{ss,A})E(c_{ss,B}) + \varepsilon \\ \varepsilon &\sim N(0,\sigma^2) \end{aligned} \quad (1)$$

where $E(c_{ss,A}, c_{ss,B})$ is the measured pharmacodynamic response, E_0 is the baseline effect, $E_{max,A}$ and $E_{max,B}$ are the maximum drug effects for drug A and drug B respectively, $c_{ss,A}$ and $c_{ss,B}$ are the steady-state concentrations for drug A and drug B respectively, $EC_{50,A}$ and $EC_{50,B}$ are the steady-state concentrations leading to half maximal effect for drug A and drug B respectively, γ_A and γ_B are the Hill coefficients for drug A and drug B respectively, α (Alpha) is the pharmacodynamic interaction parameter, and σ^2 is the residual variance. When alpha equals zero, the drugs are assumed to not have any pharmacodynamic interactions (case of additivity), whereas deviations from zero denote the cases of positive and negative interaction effects.

Summary exposure measures were obtained using the analytical solution for average steady-state concentration (c_{ss}) assuming standard linear pharmacokinetics following repeated extravascular dosing:

$$c_{ss}(\text{Dose}) = \frac{\text{Dose}\cdot F}{CL\cdot\tau} \quad (2)$$

where CL is the drug clearance, F is the bioavailability, and τ is the dosing interval. For simplicity, the apparent clearance (CL/F) and the dosing interval for both drugs were considered to be equal to CL/F = 10 L/h and τ = 24 h respectively. The variability in clearance was assumed to be log-normally distributed with standard deviation 25% for both drugs. It was further assumed that no pharmacokinetic interactions were present between the two compounds.

When drug combinations enter the clinical development phase, it is usual that the E-R profile of at least one of the mono-components has already been well characterized, meaning that the corresponding model parameters may be assumed to be known *a priori* (6). Thus, optimal designs were obtained for either estimating drug parameters of both drugs (drugs A and B; full model) or for estimating only the drug parameters of the unknown mono-component (drug B; reduced model) and potential drug interaction parameters.

Exposure-Response Profiles

Four general E-R profiles were used as examples to showcase the potential of using OD methodology for improving study designs for drug combination dose-finding studies (6). In scenario 1, drug A and drug B, described via a sigmoidal E_{max} and an E_{max} model respectively, are assumed to have a positive pharmacodynamic interaction. In scenario 2, both drugs are assumed to be described by E_{max} models, to be equally efficacious as monotherapies and to have no pharmacodynamic interactions. In scenario 3, the interaction and maximal effects of drugs A and B are the similar as the ones in scenario 1, with the difference that drug A is described via an E_{max} rather than a sigmoidal E_{max} model. Finally, in scenario 4, drug B is assumed to be 25% more efficacious than drug A ($E_{max,B} = 1.25 \times E_{max,A}$) and that there is a small negative pharmacodynamic interaction between the two. A detailed presentation of the chosen parameter values is provided as supplementary information (Supplemental Material 1).

Reference Study Design

The reference design was assumed to be a 3×3 factorial design (6). Sample size calculations were performed for the reference design, based on a power calculation using a two-sided t test, to best reflect the most common method for obtaining the sample size in dose-finding trials (16). The number of subjects needed to detect a relevant effect level (difference from placebo, $\Delta = 5\%$), with a significance level of $\alpha = 0.05$ and power of 95%, was 60 subjects per treatment arm, thus leading to a total of 540 subjects. The maximum

combination dose in the design space was assumed to be the maximum tolerated combination dose identified in the preceding first-in-human (phase I) trial.

Design Optimization

The optimal design software PopED (R package version 0.4.0) was used for the evaluation and optimization of the designs (14). PopED uses the Fisher information matrix (FIM) in tandem with a chosen optimality criterion to optimize the design variables. The FIM is defined as the negative expectation of the second-order partial derivatives of the log-likelihood function (LL) with respect to the expected parameters of a model (Eq. 1):

$$\mathbf{FIM}(\xi,\Theta) = -\mathrm{E}\left[\frac{\partial^2 \mathrm{LL}(\xi,\Theta)}{\partial\Theta\partial\Theta^{\mathrm{T}}}\right] \quad (3)$$

where $\Theta = (\theta, \sigma^2)$ is the vector of parameters to be estimated (θ-structural model parameters; σ^2 residual variability) and ξ is the vector of design variables (i.e., the monotherapy and combination dose levels). According to the Cramer-Rao inequality (Eq. 2), the FIM is an asymptotic lower bound for the precision of any unbiased maximum likelihood estimator:

$$\mathbf{COV}(\xi,\Theta) \geq \mathbf{FIM}(\xi,\Theta)^{-1} \quad (4)$$

where COV is the model variance-covariance matrix. Since the FIM is an asymptote, the precision of a model's estimated parameters in any experiment will be higher than, and asymptotically approach $\mathbf{FIM}(\xi,\Theta)^{-1}$ (16).

Design optimization was performed for six different optimality criteria (i.e., D-, D/V-, ED-, Ds, Ds/V-, and EDs-), all with respect to dose allocation. Both monotherapy and combination doses were allowed to vary. All optimizations were initiated from the reference design, apart from the E-family optimizations, which were initiated from the corresponding D- or Ds-optimal designs. The doses that were available to the search algorithm ranged from 0 to 10 mg for both drugs, within a search grid of resolution of 0.1 mg.

D- and Ds-Optimality Criteria

D-optimality was used with the full model to maximize the determinant of its FIM (equivalent to minimizing the inverse of the determinant of the FIM), thus minimizing the uncertainty of all model parameters (D_{crit}, eq. S1, Supplemental Material 2). Ds-optimality (Ds_{crit},eq. S2, Supplemental Material 2) was used with the reduced model, for optimizations where the baseline effect value (E_0, Eq. 1) was deemed to be of less interest as compared with the rest of the model parameters (14).

V-Optimality Criterion

D- and Ds-optimality criteria focus on improving the precision of model parameters. In order to improve the confidence in selecting appropriate phase III doses, one may be more interested in maximizing the information of the effect predictions at a specific region of the E-R surface (Eq. 1), which is equivalent to minimizing the model prediction variance within a specific region. Optimizations based on V-optimality (V_{crit}, eq. S3, Supplemental Material 2) rely on the definition of an interesting part of the E-R surface, around which the uncertainty of the model predictions should be minimized (15,16). To define this region, first, the true MEC leading to a chosen target effect level ($\Delta_{Target} = 10\%$ in this work) was derived using the true model parameters for each scenario. Subsequently, the interesting region was defined as a square in the two-dimensional space that encloses the true MEC within ± 7.5 ng/mL ($c_{ss,max/min} = c_{ss} \pm 7.5$ ng/mL).

Compound Criteria

To ensure both benefits of D-optimality for the overall parameter precision and V-optimality for precision around specific portions of the E-R surface important for a development decision, a compound criterion was constructed where D(s)- and V-optimality are considered simultaneously. Designs based on this compound criterion should be efficient both for estimating the model parameters of interest while having an additional focus on minimizing the prediction interval in a relevant region of the E-R surface. Such designs maximize the expression:

$$D(s)/V_{\mathrm{crit}}(\xi,\Theta) = \kappa \cdot \log D(s)_{\mathrm{crit}}(\xi,\Theta) + (1-\kappa)\cdot V_{\mathrm{crit}}(\xi,\Theta) \quad (5)$$

where $D(s)_{crit}$ (eq. S1 and S2, Supplemental Material 2) and V_{crit} (eq. S4, Supplemental Material 2) are the D(s)- and V-optimality criteria respectively and κ is an integer ($0 \leq \kappa \leq 1$) that controls how much each design criterion influences the final design. A D/V-criterion with κ close to 1 would lead to designs approaching D-optimality, while a D/V criterion with κ close to 0 would lead to designs approaching V-optimality. In this work, κ was set to 0.5 throughout (equal contribution from the D(s)- and V-criterions).

Global Optimal Designs

For all optimality criteria presented above, the optimizations were based on the FIM, which for nonlinear models is dependent on the parameter vector Θ (16). Thus, the obtained designs will be optimal for that set of parameter values alone (local optimal designs). Global optimal designs can be constructed to be optimal for a distribution of parameter values, i.e., when there is uncertainty in the parameter space (17), which is often considerable during design of dose-ranging studies. Here, E-family optimal designs using uniform distributions for parameter values were computed (eq. S5 and S6, Supplemental Material 2). The uniform distributions were constructed such that the parameter values of all investigated scenarios were included (Table S1, Supplemental Material 1).

Minimum Effective Combination Dose

Because the E-R relationship of a combination treatment is described by a response surface, a plethora of combined

exposure pairs can lead to the same effect, which is known as the isoeffective isobole (11,18). However, typically only one combination pair is desirable to be brought forward to confirmatory trials. Thus, for a target effect level, the desired combination pair was assumed to be the one that simultaneously minimizes the squared sum of the c_{ss} of both drugs (combined minimum effective concentration; $MEC_{A,B}$) (5):

$$MEC(c_{ss,A}, c_{ss,B}) = \sqrt{c_{ss,B}^2 + c_{ss,A}^2} \quad (6)$$

The minimum effective dose (MED) for each compound can then be derived from the c_{ss} for that compound (Eq. 2).

DESIGN EVALUATION

Efficiency

Efficiency is a metric that can be used for the comparison of two different designs and is a measure of how much information is contained in a design as compared with another (16). Here, D- and Ds-efficiency were used to compare the reference design to the optimized ones:

$$\mathrm{Eff}_D(\xi, \Theta) = \left(\frac{|\boldsymbol{FIM}(\xi, \Theta)|}{|\boldsymbol{FIM}(\xi^*, \Theta)|}\right)^{1/p} \times 100\% \quad (7)$$

where ξ^* and ξ are the vectors for the optimized and original designs respectively and p is the number of parameters of the model.

$$\mathrm{Eff}_{Ds}(\xi, \Theta) = \left(\frac{|\boldsymbol{FIM}_{\mathrm{Full}}(\xi,\Theta)| \,/\, |\boldsymbol{FIM}_{Rdc}(\xi,\Theta)|}{|\boldsymbol{FIM}_{\mathrm{Full}}(\xi^*,\Theta)| \,/\, |\boldsymbol{FIM}_{Rdc}(\xi^*,\Theta)|}\right)^{1/p_s} \times 100\% \quad (8)$$

where $\boldsymbol{FIM}_{\mathrm{Full}}$ is the FIM of all model parameters and $\boldsymbol{FIM}_{Rdc}$is the FIM of only the parameters that are considered to be not of interest and p_s the number of interesting parameters. A useful interpretation is in terms of how many more individuals would be needed in a trial based on a reference design to match the characteristics (e.g., parameter precision) of an optimized one. For instance, an efficiency measure of 150% suggests that an optimized design would need 50% less individuals as compared with the reference for obtaining parameter estimates with equal precision.

Parameter Accuracy and Precision

Stochastic simulation and estimation (SSE) was performed to obtain parameter accuracy and precision for the reference and the optimized designs. For each scenario, 1000 datasets were simulated and estimated using the PDiM. SSE was performed using PsN (19) and NONMEM version 7.3 (20). Parameter estimation was based on the least squares method (FO estimation method in NONMEM, in this case equivalent to FOCE(I), as no random effects were included in the model). The estimated parameters were summarized and accuracy (Bias) and precision (%RSE) were computed as follows:

$$\mathrm{BIAS}\left(\theta_j\right) = \frac{1}{N}\left[\sum_{i=1}^{N} \frac{\hat{\theta}_j - \theta_j}{\theta_j}\right] \times 100\% \quad (9)$$

$$\%\mathrm{RSE}\left(\hat{\theta}_j\right) = \frac{\mathrm{sd}}{\theta} \times 100\% \quad (10)$$

where $\hat{\theta}_j$ denotes the estimated jth model parameter value for the ith simulation, θ_j is the true jth parameter value used in the initial simulations, and N is the number of simulations ($N = 1000$). Overall parameter bias and precision were defined as the average bias and precision across all parameter estimates.

Model Prediction Uncertainty

The influence of study design on the uncertainty around the model predictions was explored by comparing the model predictions obtained by the optimized designs with ones obtained by the reference design. 95% confidence intervals (CIs) around the entire E-R relationships were approximated by the delta method, using the FIM-derived covariance matrix (21). For the interesting region of the E-R relationships and for each concentration pair, the lower CIs were subtracted from the upper ones, resulting in a metric of the width of the CIs. Subsequently, the median of these values was divided by the one obtained for the reference study design resulting in a CI ratio for the interesting region of the curve ($\mathrm{CI}_{\mathrm{Ratio,Region}}$; $\mathrm{CI}_{\mathrm{RR}}$).

Correct Dose Identification

To assess the ability of the optimized designs to increase confidence in dose selection as compared with the reference design, the probability of identifying the correct MED was evaluated. Using the SSE-derived parameter vectors, the $\mathrm{MED}_{A,B}$ targeting a range of Δ_{Target} (1–13%) were found and the probabilities of identification of the correct combination dose ($\mathrm{MED}_{A,B}$) were derived (where correct is assumed to be a dose that is within 20% of the true $\mathrm{MED}_{A,B}$).

RESULTS

The evaluated E-R profiles of the four different scenarios are presented in Fig. 1. Figure 2 presents the reference and global optimal designs and Fig. 3 presents the local optimal designs for the different scenarios and optimizations. Table I presents the D(s)-efficiency, overall parameter accuracy and precision, and the $\mathrm{CI}_{\mathrm{RR}}$ for the competing designs.

Efficiency

All optimized designs were compared with the reference design in regard to their D- and Ds-efficiency for estimating the model parameters under the full and reduced model, respectively. Regarding the full model, the D-efficiency of the

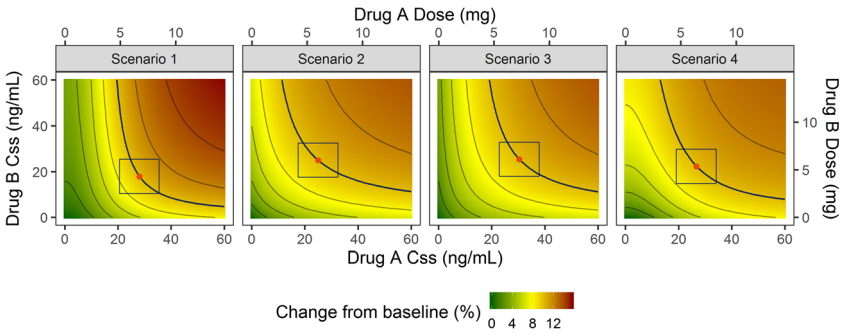

Fig. 1. Response surfaces of the four studied exposure-response relationships. Grey contour lines represent different effect levels. The highlighted blue contour line represents the concentration pairs leading to a target effect level (ΔTarget = 10%). The red point represents the optimal combination concentration (MEC), where the required exposure of Drug A and Drug B are simultaneously minimized. The grey square enclosing the red point represents the area of interest for minimizing the prediction variance

D-optimal designs ranged from 116.3 to 7831.8%. When designs were optimized using the D/V-optimality criterion, the D-efficiency was slightly lower than the D-optimal designs, ranging from 97.7 (scenario 2) to 7168.7%. The D-efficiency of the globally optimal design (common design for all scenarios) ranged between 87.2 (scenario 3) and 7117% as compared with the reference design.

When designs were optimized for the reduced model under the Ds-optimality criterion, the Ds-efficiency obtained or the four scenarios ranged between 123.4 and 151.1%. The Ds/V optimal designs resulted in moderately lower Ds-efficiency, ranging between 96.2 and 130.6%. Lastly, the EDs-optimal design led to Ds-efficiencies of 91.3 to 127.2%.

Parameter Accuracy and Precision

As shown in Table I, the use of the factorial (reference) design and analysis with the full model led to a markedly poor performance in regard to parameter accuracy and precision, especially for scenarios 1 and 4. In agreement with the efficiency results, optimization of the allocation of the combination doses led to a clear improvement of the overall parameter accuracy and precision across all locally optimal designs. For the ED-optimal design, there was improvement in accuracy and bias for three of the four scenarios, with scenario 3 resulting in somewhat worse results. As expected, compared with the D-optimal designs, some loss in parameter precision was observed for D/V-optimal designs with the most pronounced difference in average %RSE seen for scenario 4 (D, 32.5%; D/V, 510.7%).

For all scenarios, the reduced model, allowed for reasonable parameter estimation with the factorial (reference) design, matching results seen previously (6). The Ds-optimal and Ds/V-optimal designs moderately improved the parameter bias and %RSE, while the EDs-design could either moderately improve or worsen the bias and %RSE compared with the reference designs.

Overall, unbiased parameter estimates were found for all optimized designs, which was not always the case for the reference designs. The SSE derived %RSE for each parameter individually, across all scenarios and optimizations are provided as supplementary information (Table S2,

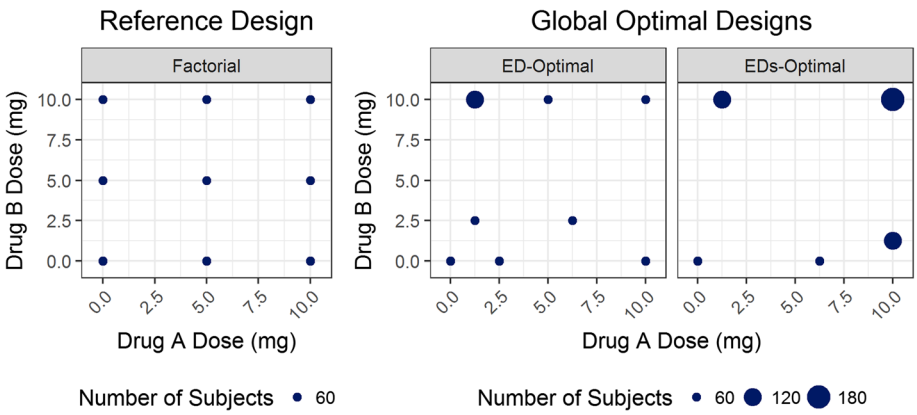

Fig. 2. The reference design, similar to ones typically used in dose-finding studies (left) and the global optimal designs (right). The reference design was a 3 × 3 factorial, consisting of nine cohorts (one placebo, two for each of the mono-components and four combination levels). The ED-optimal design was constructed using the Full Model and the EDs-Optimal design was constructed using the Reduced Model. The dose levels are represented by blue points with a varying size corresponding to the number of subjects per treatment. Five hundred forty subjects were included in all designs

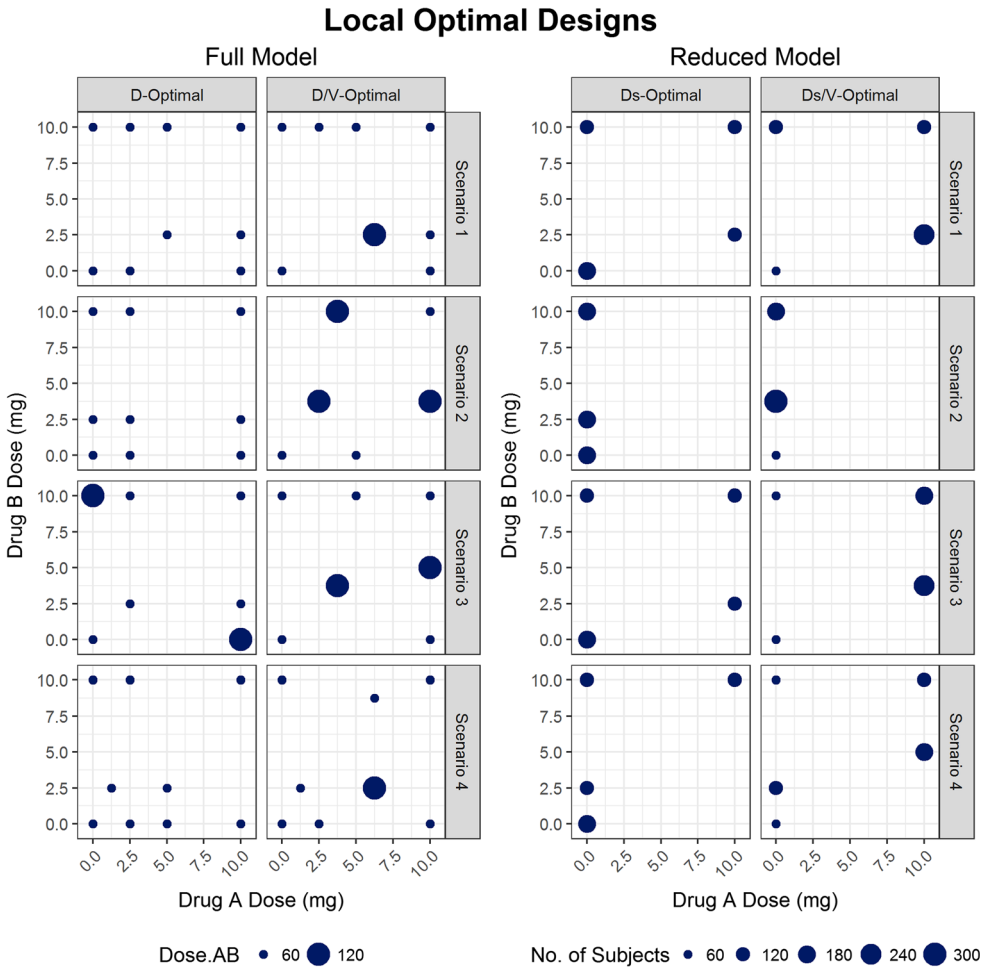

Fig. 3. Local D- and D/V-optimal designs, constructed using the Full Model (left) and Ds- and Ds/V-optimal designs, constructed using the Reduced Model (right). The dose levels are represented by blue points with a varying size corresponding to the number of subjects per treatment. The D(s)/V-optimal designs were constructed for a pre-specified target effect level (ΔTarget = 10%). Five hundred forty subjects were included in all designs

Supplemental Material 3).

Uncertainty in Model Predictions

For the full model, the CI_{RR} in Table I of the D-optimal designs as compared with the reference design, ranged between 0.9 and 1.05%, meaning that the response surface CIs, in the relevant target effect area, were up to 10% wider than from the reference design. Scenario 1 was the only case where the CIs were tighter for the D-optimal design as compared with the reference design. The CI_{RR} were markedly improved for all D/V-optimal designs (ranging between 1.07 and 1.33), meaning that the CIs of the response surfaces were between 7 and 33% tighter than for the reference design. All ED-optimal designs had a CI_{RR} smaller than 1 (ranging between 0.85 and 0.98) meaning that the model predictions were wider by 2 to 15% as compared with the reference design. Similar trends could be observed for the optimizations concerning the reduced model. The largest CI_{RR} were observed for the Ds/V-optimal designs, which ranged between 1.48 and 1.78.

Figure 4 presents the drug-combination E-R surface 95% confidence interval widths, for the four evaluated scenarios under the reference design and the different optimization methods, against steady-state concentrations of either drug A or drug B. It can be seen that when D(s)/V-optimizations were performed, the CIs' width was consistently reduced in the relevant target effect regions.

Correct Dose Identification

The probabilities of identifying the correct dose (within 20% of the true $MED_{A,B}$) for the different scenarios and optimizations are shown in Fig. 5. A similar trend of increasing probability until approximately $\Delta_{Target} = 10\%$ was observed for almost all scenarios and optimizations. In general, for $\Delta_{Target} = 10\%$, the D(s)/V optimal designs led to the highest probability of correct $MED_{A,B}$ identification [D/V, 69.4–84.7%; Ds/V, 87.8–94.9%], followed by D(s) [D, 57.4–78.6%; Ds, 76.7–87%], ED(s) [ED, 57–72.8%; EDs, 71.7–82.3%] and the reference design [full model, 54.7–63.7%; reduced model, 62.7–79.6%].

Table I. D(s)-Efficiency, Average Estimated Relative Standard Error (%RSE), and Parameter Accuracy (Bias (%)) and Confidence Interval Ratio for the Interesting Region of the Curve Around the Target Effect (CI_{RR}) for the Four Different E-R Scenarios and Optimized Designs

	Design	D(s)-efficiency (%)	Average %RSE	Average bias (%)	CI_{RR}
Full model	Scenario 1				
	Factorial (reference)	–	452	21.8	1
	D-optimal	7322.6	25.7	3.9	1.05
	D/V-optimal	6913.8	28.7	4.6	1.33
	ED-optimal	6065	33.7	6.7	0.98
	Scenario 2				
	Factorial (reference)	–	20.5	2.8	1
	D-optimal	122.4	17	2.4	0.93
	D/V-optimal	97.7	19.1	3.1	1.12
	ED-optimal	100.3	20.5	3.8	0.9
	Scenario 3				
	Factorial (reference)	–	29.5	4.4	1
	D-optimal	116.3	26.3	4	0.9
	D/V-optimal	104.9	29	4.5	1.07
	ED-optimal	87.2	149.1	16.7	0.85
	Scenario 4				
	Factorial (reference)	–	> 1000	> 1000	1
	D-optimal	7831.8	32.5	4.3	0.96
	D/V-optimal	7168.7	510.7	21.1	1.18
	ED-optimal	7117	291	14.1	0.92
Reduced model	Scenario 1				
	Factorial	–	16.1	2.3	1
	Ds-optimal	151.1	12.4	1.7	1.24
	Ds/V-optimal	130.6	13.9	1.8	1.67
	EDs-optimal	127.2	14.6	2.4	0.93
	Scenario 2				
	Factorial	–	10.9	1.6	1
	Ds-optimal	123.4	8.9	1.1	1.05
	Ds/V-optimal	96.2	10	1.1	1.34
	EDs-optimal	99.3	11.4	2.2	0.89
	Scenario 3				
	Factorial	–	17.3	2.6	1
	Ds-optimal	141.2	13.6	2	1.06
	Ds/V-optimal	107.5	16.1	2	1.38
	EDs-optimal	98.7	17.9	3.2	0.93
	Scenario 4				
	Factorial	–	11.4	1.4	1
	Ds-optimal	146.9	8.9	0.5	1.11
	Ds/V-optimal	107.7	10.7	1	1.46
	EDs-optimal	91.3	13.1	2.3	0.89

Computations for CI_{RR} were all done for the area of interest around the target effect level ($\Delta_{Target} = 10\%$). All comparisons were made with the corresponding reference trial and the same model (i.e., full or reduced model)

DISCUSSION

Drug combinations are increasingly being considered as a viable strategy for increasing the efficiency of pharmacotherapeutic treatments in various medical fields (3). While the notion of combining more than one drug has a sound pharmacological basis, the clinical development of such treatments and especially the dose-finding phase can be substantially more challenging than for single-drug treatments (6). Thus, there is a need for developing methods that can help identify which dose levels to investigate, in order to maximize the information retrieved from a clinical program. In this work, a variety of realistic combinatory E-R profiles were used as general examples to highlight the importance of using optimal design methodology for guiding the allocation of studied doses. To our knowledge, this is the first study that investigates how optimal design methodology can be used for improving the outcome of the E-R analyses in combination dose-finding trials.

Substantial issues became evident when a typical factorial design was used. Poor performance was observed in regard to parameter accuracy and precision, especially for scenarios 1 and 4, which would likely hinder the credibility of a model-based analysis in a real-world setting. When optimizing designs for the full model with the D-optimality criterion, it was possible to improve the overall precision of the parameters between 10.8 and 96.6% and substantially improve the efficiency (up to $Eff_D = 7831.8\%$). Smaller gains were observed when designs were optimized for the reduced

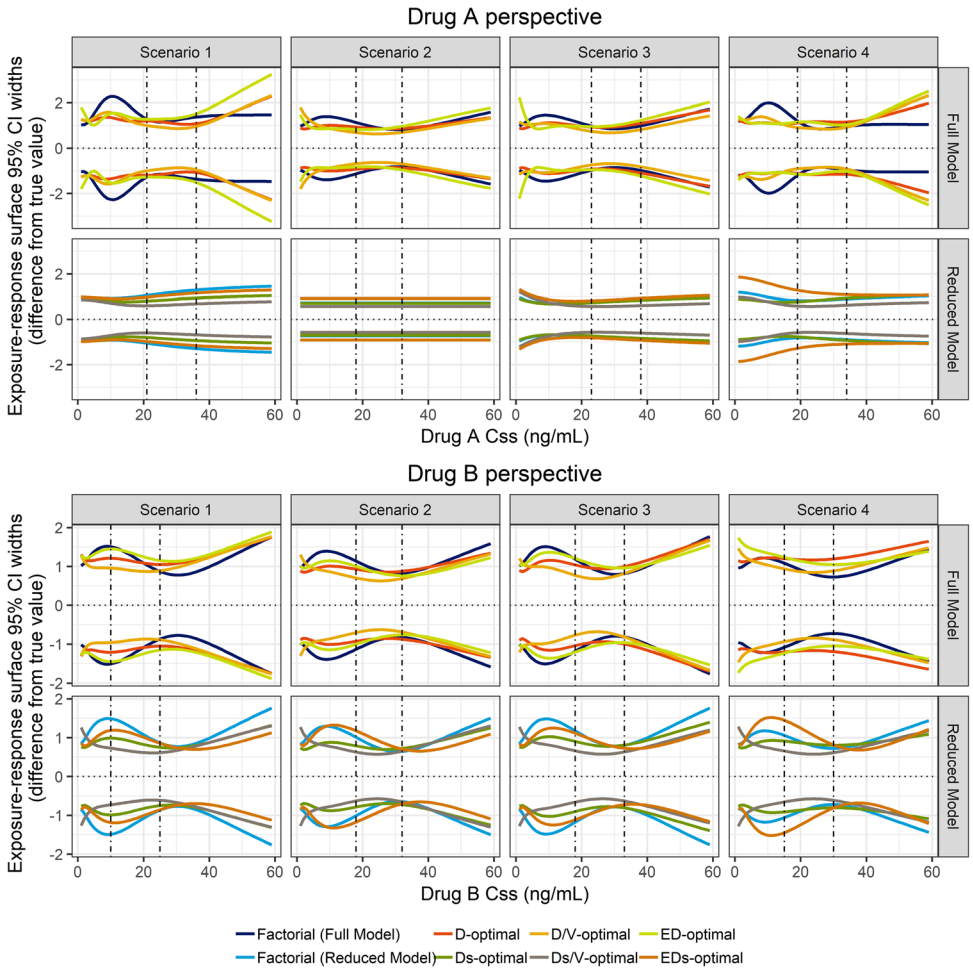

Fig. 4. Exposure-response surface 95% confidence interval (CI) widths for the four evaluated scenarios under the reference design and the different optimization methods, against the steady-state concentrations of Drug A (top) and Drug B (bottom). The confidence intervals were derived using the delta method and the FIM derived covariance matrix and their widths were constructed by subtracting the 2.5th and 97.5th percentile from the true value. All presented Drug A or Drug B concentrations are combinations with the mean Drug B and Drug A concentrations, respectively, that define the area of interest for minimizing the prediction variance (represented by the vertical dotted lines)

model and the Ds-optimality criterion, where Eff_{Ds} ranged between 123.4 and 151.1%. These results, when taken together, imply that it is challenging to rely on the full model approaches combined with standard trial designs (6) and that the reduced model, due to the smaller number of estimable parameters, may be a more reliable approach for combination E-R analyses if optimization is not performed. In any case, the optimized designs significantly improved the retrieved amount of information.

Despite the clear improvement in parameter estimation in all D-optimal designs and across all scenarios, the CI_{RR} typically moved in the opposite direction, where an increase of up to 10% of the width of the CIs was observed in the optimized designs as compared with the reference in the region of interest. This highlights the importance of taking model predictions into consideration when making decisions regarding which design to take forward, as D-optimal designs failed to produce more accurate predictions for the specific region of interest. For the reduced model, the same trend was not observed for the Ds-optimal designs, where the CI_{RR} was improved between 5 and 24% as compared with the reference in the region of interest.

Since the goal of dose-finding studies is to identify the best doses to be brought forward to late-stage development, good precision around a target effect level (i.e., CI_{RR}) is highly desirable. In the case of single-drug therapies, where the treatment response is driven by a sole variable (i.e., exposure of a single drug), trial optimization towards this goal can be achieved by either approaching the target exposure level as a model parameter with uncertainty that should be minimized (22) or by constructing designs that minimize the asymptotic variance of the target concentration estimates (22). For drug combinations, such approaches are complicated by the fact that the treatment effect is driven by the combination of two variables (i.e., exposures of drug A and drug B). The approach used here was to utilize an optimality criterion that aims to reduce the average prediction variance in a specific region of the three-dimensional E-R surface (V-Optimality) (23). A target effect level is necessary for the definition of such a region and the volume of this region can

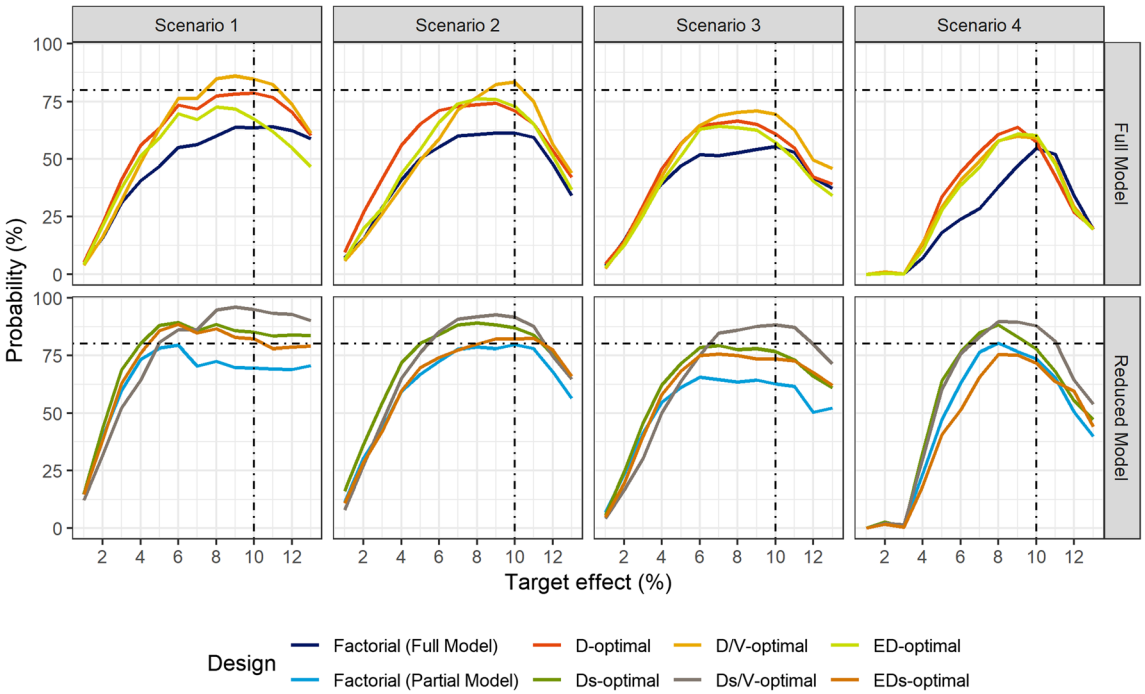

Fig. 5. Probabilities that the estimated MEDA,B are within 20% of the true MEDA,B for different target effect levels evaluated under the reference and optimized designs. The vertical dotted line represents the target effect level (ΔTarget = 10%)

be decided *a priori*. Here, an arbitrary level was used throughout, but in cases where a tight prediction is wanted in a very specific area, this can be adjusted accordingly.

V-Optimal designs can be hard to construct (15,24) and generally lead to poor parameter estimation (15), which is undesirable when performing a model-based analysis. This can be mitigated by the use of a compound metric incorporating D(s)-optimality characteristics (D(s)/V-optimality). In this work, equal contribution from the D(s)- and V-optimality criteria was used throughout, in order to obtain designs that refrain from substantially reducing the quality of the parameter estimates. Significant gains in CI_{RR} were found for the D/V-optimal designs, which ranged between 7 and 33% compared with the D- and 34 to 67% compared with the Ds-optimal designs. Very little loss in parameter precision as compared with the D(s)-optimal designs was observed (%RSE increase between 11.6 and 20.2%), except for scenario 4, where the D/V-optimal design led to 14.7 times worse parameter precision than its D-optimal counterpart.

When designs were optimized, some clustering of dose levels was observed, because some regions of the design space bear substantially more information than others. This can be used for reducing the number of cohorts included in the trial, which may be beneficial from a clinical operations point of view. This was most evident for designs that were optimized for the reduced model, where four or five dose levels were appropriate (in contrast to the nine dose levels used in the reference design). Interestingly, these smaller trials were up to 51.1% more Ds-efficient than the reference design, meaning that enrolling 270 subjects in the optimized design would yield the same amount of information as 540 subjects would in the reference design. In some cases, especially when the full model was used, D-efficiency exceeded 1000%. It should be noted that these very large gains in efficiency should be attributed to the uninformative nature of the reference design, which rendered parts of the model not estimable, and should thus not be directly related to needed number of individuals to obtain the same amount of information.

The feasibility of a proposed design, in terms of logistics and acceptability from the regulatory authorities, is of paramount importance. The cohort allocation based on the D- and D/V- optimality criteria was characterized by substantial scatter within the design space, which was very sensitive to the chosen parameters. Such designs would not be appropriate for standard statistical analyses, such as pairwise group comparisons, which remain an important part of the clinical development process. This, taken together with the inherent drawback of local optimal designs (optimal for only the set of parameters that the designs are based on), highlights that choosing any of the presented D- or D/V-optimal designs could pose an unacceptable risk for the clinical development team. In contrast, the Ds- and Ds/V-optimal designs were less sensitive to the model parameters and more similar across different scenarios, once again highlighting the relevance of using the reduced model.

It has to be noted that the results presented here (i.e., the magnitude of the efficiency gains of the optimized designs *versus* the typical design and the allocation of the combination doses) are directly related to the chosen model structure and parameter values, meaning that they are not intended as a general recommendation for dose-allocation in drug-combination dose-finding studies, but instead as an example of how optimal design methodology can be applied for improving the probability of success of drug combination dose-finding trials. Because each clinical development

program is unique, such optimizations (i.e., model structure, parameter values, and their uncertainty) should be tailored to the program at hand, based on previous understanding of the system from preclinical data and prior clinical trials.

A variety of pharmacodynamic interaction models have been previously developed, to characterize symmetric (i.e., concentration independent) or asymmetric (i.e., concentration dependent) pharmacodynamic interactions (5,11,25–27). Even though such models have the potential to describe high-dimensional interactions, their applicability to clinical data may be hindered due to the inherent large variability in the measured pharmacodynamic response. To mitigate this, here we have used a relatively simple interaction model that adheres to the parsimony principle (i.e., only one interaction parameter needs to be estimated). It must be noted, however, that the presented model structure is not intended as a general recommendation for the analysis of clinical drug combination data, and that clinical trial optimizations should be performed using interaction models that have previously been developed for each specific drug-combination under clinical development (e.g., through a systematic model building process).

To mitigate the risks of relying on local optimal designs (i.e., the parameter values of novel compounds are not known *a priori*), different global optimality criteria can be used. Here, the potential uncertainty in parameter values was accounted for, using the ED(s)-optimal criterion (17). In order to obtain a single-study design that could be used interchangeably for all investigated E-R scenarios, we chose to represent the uncertainty with a uniform distribution that spans across the parameter space of all scenarios. Alternatively, normal or log-normal distributions of parameter uncertainty, usually derived from uncertainty estimates from earlier clinical (i.e., phase I) or preclinical trials, could have been used. Such global designs are expected to yield even higher efficiency than the ones presented here, due to the fact that they are more tailored for the development program at hand. In the current setting, the global designs perform well compared with the reference designs in terms of parameter precision, but perform somewhat worse in terms of CI_{RR}. This is expected as the global design should have similar operating characteristics of the local design it is integrating parameter distributions across (the D-optimal designs, generally, performed somewhat worse in terms of CI_{RR}). Although not computed here, there is no theoretical hinder to computing, for example, ED(s)/V-optimal designs.

All trials were optimized for landmark exposure-response analyses, where a single exposure metric (c_{ss}) is related to the measured pharmacodynamic effect at a single time point (10). Even though such exposure-response analyses are routinely performed for the demonstration of clinical efficacy, optimizations could also be performed for time-course models, where the individual variability in drug concentration and response is considered, potentially leading to an increase of information extraction in the expense of more complex pharmacodynamic analyses. Lastly, it was assumed here that the largest combination dose in the design space was the maximum tolerated combination dose, identified in previously performed first-in-human trials. For clinical development programs where safety may be of concern, our presented optimization methods could be extended to include utility functions that take efficacy and safety simultaneously into account (28).

CONCLUSION

In conclusion, it was shown that using optimal design in tandem with E-R analyses can be an attractive method for dose allocation in drug-combination dose-finding studies. Optimized studies significantly improved the extracted amount of information, allowing for the same information from as little as 50% of the subjects as compared with a typical drug-combination design. In addition, the flexibility in defining the optimality criteria can help improve the probability of identifying the optimal combination dose to be brought forward in late stage development. Formulating a clear study goal *a priori* is of high importance, as substantial differences between optimized designs occur depending on what information is prioritized. Future research should be directed towards evaluating the effect of using nonlinear mixed-effects models that allow the extraction of information from the entire treatment time-course, the influence of uncertainty in the combination model structure (29), as well as the added value of using novel methods, such as model-based adaptive optimal designs (28).

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