Model based optimization of dose-finding studies for drug-combinations

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Background

Combination pharmacotherapy

- Simultaneous administration of more than one drugs may
  - Enhance the efficiency of pharmacotherapy[1]
    - Higher effect compared to the two mono-components alone
  - Lead to decreased side-effects[1]
    - Smaller needed doses for each drug
- Used in various medical fields
  - Metabolic disease (Diabetes, Obesity)
  - Cancer
  - Infectious disease
  - Circulatory system disorders (Hypertension, Atherosclerosis)
  - Anaesthesiology

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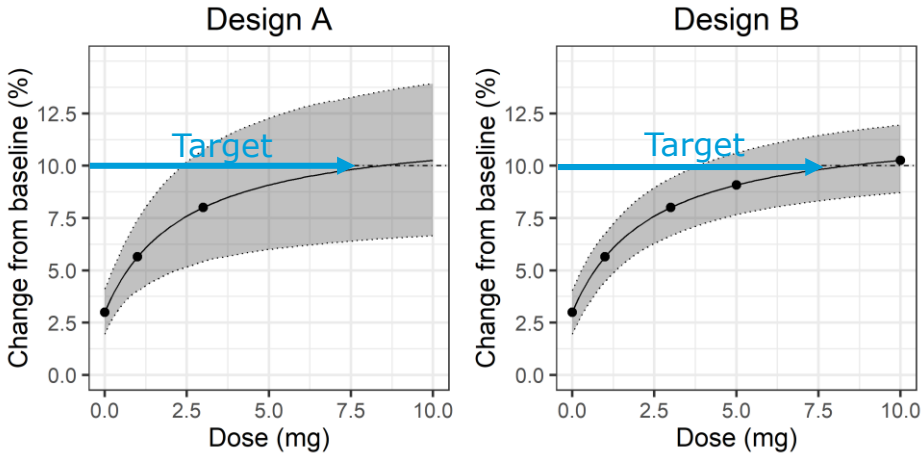
1. Bell DSH. Combine and conquer: advantages and disadvantages of fixed-dose combination therapy. Diabetes Obes Metab

Background

Dose selection in clinical drug development

- Even for single drugs, ***dose selection*** is one of the most challenging steps in drug development[1,2]
  - Poor dose selection is still an important cause of the high attrition rate in confirmatory trials[1,2]
- Accurate delineation of the *Dose–Exposure–Response* (DER) relationship is a **key** aspect for rational dose selection[1,2]



1. Musuamba FT, Manolis E, Holford N, Cheung SYA, Friberg LE, Ogungbenro K, et al. Advanced methods for dose and regimen finding during drug development: Summary of the EMA/EFPIA workshop on dose finding (London 4-5 December 2014). CPT Pharmacometrics Syst Pharmacol.
2. Report from Dose Finding Workshop European Medicines Agency, London, 04 – 05 December 2014

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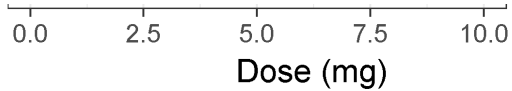
Background

Dose selection in drug combinations

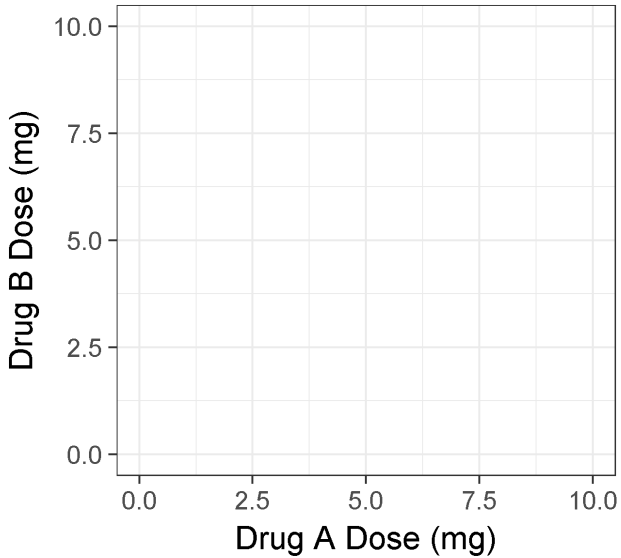
- Dose selection for single drugs is a single-dimensional problem



Background

Dose selection in drug combinations

- Dose selection for single drugs is a single-dimensional problem
- For drug combinations, there is an additional level of complexity
  - Many potential doses to explore
  - Complex Dose-Exposure-Response relationships
    - Especially when pharmacodynamic interactions are present
- Drug development challenge
  - Which combination doses should be explored in a dose-finding setting to
    - Maximize the collected information
    - Increase the probability to select a promising dose to bring forward to confirmatory trials



Aim

- Evaluate the added benefit of using **Optimal Design** for guiding the allocation of studied combination doses in a dose-finding setting
- **Compare** the optimized designs to a typical drug-combination dose-finding design in terms of **probability** to identify the most promising combination dose to bring forward to confirmatory trials

Methods

Drug characteristics and pharmacodynamic endpoint

- Two hypothetical compounds
  - Drug A: Well-established E-R relationship and approved dose
  - Drug B: Novel add-on, with unknown E-R relationship
  - Drugs administered as a 'loose' combination
    - Any combination dose could be considered
- Pharmacodynamic endpoint:
  - % change from baseline
    - Can be applied to any continuous clinical response endpoint
- Analysis method:
  - End-of-study, cross-sectional Exposure-Response (E-R) analysis

Methods

Drug exposure

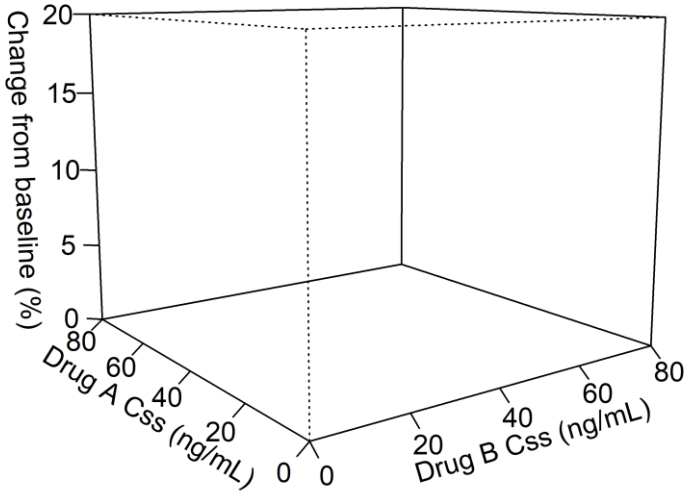
- Pharmacokinetic (PK) assumptions:
  - Population PK models for both drugs developed prior to the E-R analysis
  - No PK interactions between the two drugs
  - Average steady state concentration (C_{ss}, ng/mL) following repeated dosing
    - Assuming standard linear pharmacokinetics for both drugs

$$C_{ss,x}(Dose_x) = \frac{Dose_x \cdot F_x}{CL_{x,i} \cdot \tau} \qquad CL_{x,i} = \theta_x e^{\eta_{x,i}} \qquad \eta_{x,i} \sim N(0, \omega_x^2)$$

CL: Drug clearance
F: Bioavailability
τ: Dosing interval
The apparent clearance (CL/F) and dosing interval for both drugs were considered to be equal (CL/F=10 L/h and τ=24h)
The variability in clearance was assumed to be log-normally distributed with standard deviation 25%

Methods

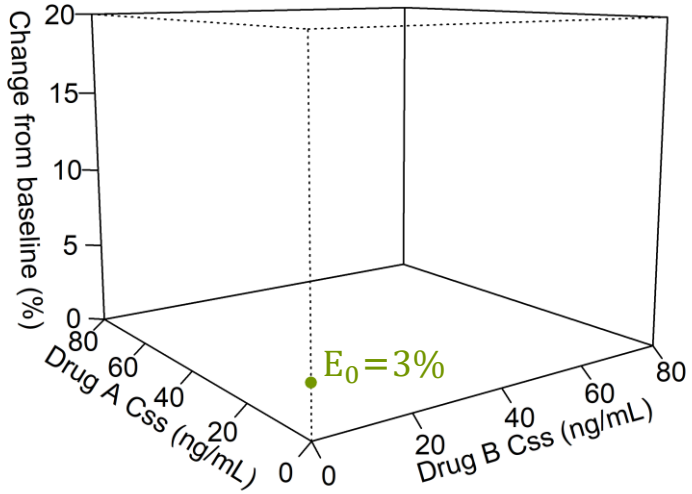
Combination Dose-Exposure-Response model



Model for empirical description of pharmacodynamic interaction data. Not **indented** for identification of deviation from additivity

Methods

Combination Dose-Exposure-Response model

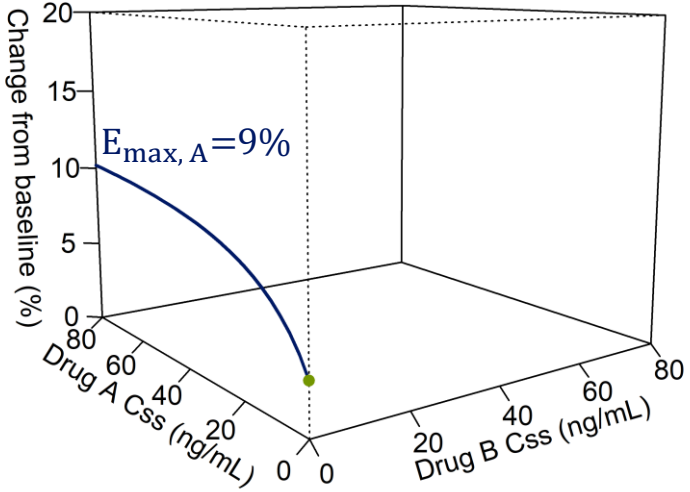


$$E = E_0$$

Model for empirical description of pharmacodynamic interaction data. Not indented for identification of deviation from additivity

Methods

Combination Dose-Exposure-Response model



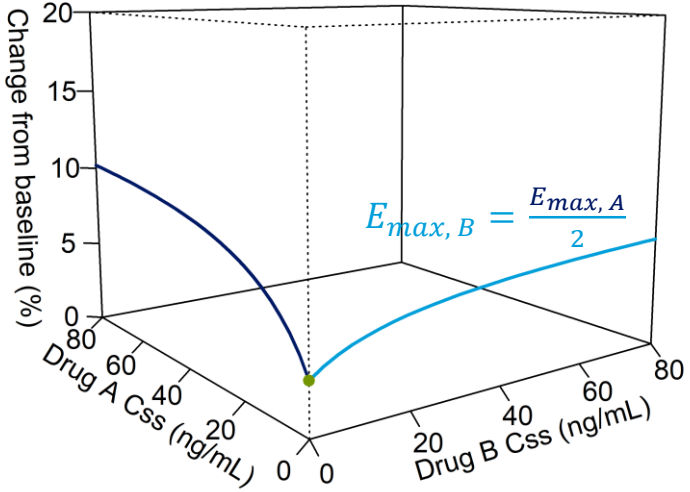
$$E_A = \frac{E_{max,\,A} \cdot {C_{ss,A}}^{\gamma_A}}{{EC_{50,\,A}}^{\gamma_A} + {C_{ss,A}}^{\gamma_A}}$$

$$E = E_0 + E_A$$

Model for empirical description of pharmacodynamic interaction data. Not indented for identification of deviation from additivity

Methods

Combination Dose-Exposure-Response model

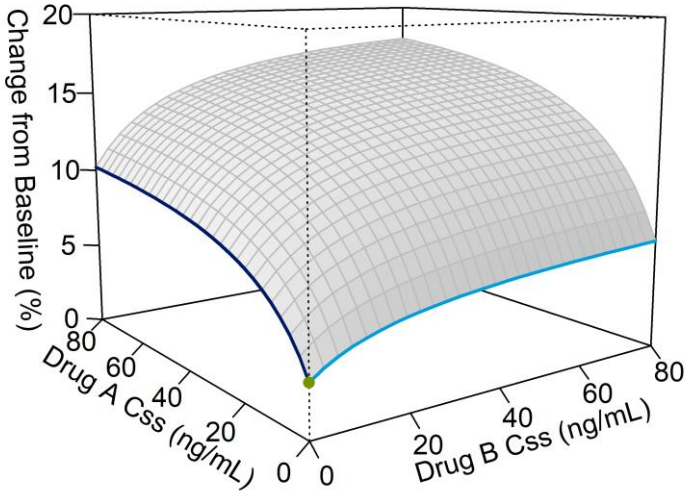


$$E_A = \frac{E_{max,\,A} \cdot {C_{ss,A}}^{\gamma_A}}{{EC_{50,\,A}}^{\gamma_A} + {C_{ss,A}}^{\gamma_A}} \qquad E_B = \frac{E_{max,\,B} \cdot {C_{ss,B}}^{\gamma_B}}{{EC_{50,\,B}}^{\gamma_B} + {C_{ss,B}}^{\gamma_B}}$$

$$E = E_0 + E_A + E_B$$

Methods

Combination Dose-Exposure-Response model



$$E_A = \frac{E_{Max,A} \cdot {C_{ss,A}}^{\gamma_A}}{{EC_{50,A}}^{\gamma_A} + {C_{ss,A}}^{\gamma_A}} \qquad E_B = \frac{E_{max,B} \cdot {C_{ss,B}}^{\gamma_B}}{{EC_{50,B}}^{\gamma_B} + {C_{ss,B}}^{\gamma_B}}$$

$$E = E_0 + E_A + E_B + \alpha E_A E_B + \varepsilon, \qquad \varepsilon \sim N(0, \sigma^2)$$

$$a = \begin{cases} Positive\ Interaction, & a > 0 \\ Lack\ of\ Interaction, & a = 0 \\ Negative\ Interaction, & a < 0 \end{cases}$$

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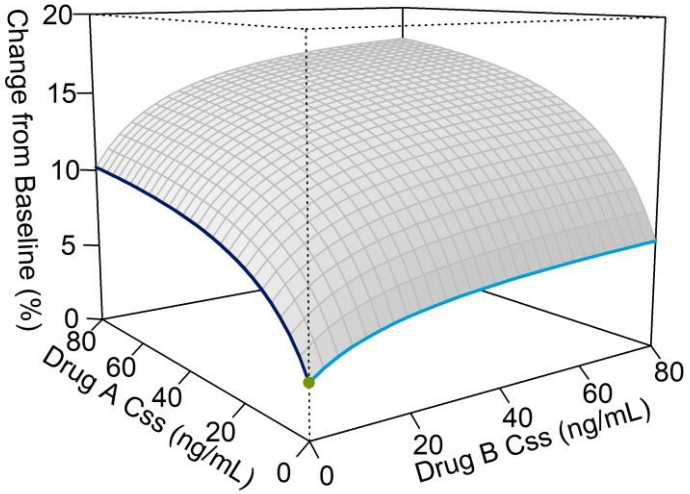
Model for empirical description of pharmacodynamic interaction data. Not intended for identification of deviation from additivity

Methods

Combination Dose-Exposure-Response model



$$E_A = \frac{E_{Max,A} \cdot {C_{ss,A}}^{\gamma_A}}{{EC_{50,A}}^{\gamma_A} + {C_{ss,A}}^{\gamma_A}} \qquad E_B = \frac{E_{max,B} \cdot {C_{ss,B}}^{\gamma_B}}{{EC_{50,B}}^{\gamma_B} + {C_{ss,B}}^{\gamma_B}}$$

$$E = E_0 + E_A + E_B + \alpha E_A E_B + \varepsilon, \qquad \varepsilon \sim N(0, \sigma^2)$$

$$a = \begin{cases} \textbf{\textit{Positive Interaction}}, & a > 0 \\ \textit{Lack of Interaction}, & a = 0 \\ \textit{Negative Interaction}, & a < 0 \end{cases}$$

a=0.15

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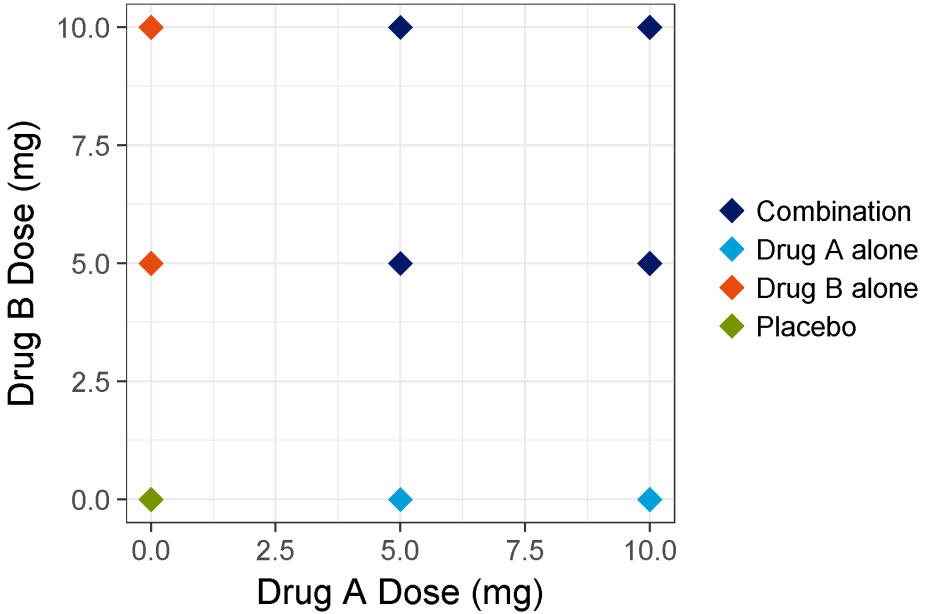
Model for empirical description of pharmacodynamic interaction data. Not intended for identification of deviation from additivity

Methods

Reference design (3x3 factorial)

- Most comprehensive design found in the literature[1]
  - Simple construction
  - Ignores potential differences in the information in the design space
- N_{trial}=540 subjects (60 subjects per arm)
  - Power calculation using a two-sided t-test
    - Reflects the most common method for obtaining the sample size in dose finding trials
    - Powered to detect a Δ=5% from placebo



Level of variance: 6% sd. 95% power. 95% significance level of α = 0.05

1. Nøhr-Nielsen A, De Bruin ML, Thomsen M, Pipper CB, Lange T, Bjerrum OJ, et al. Body of evidence and approaches applied in the clinical development program of fixed-dose combinations in the European Union from 2010-2016. Br J Clin Pharmacol. 2019

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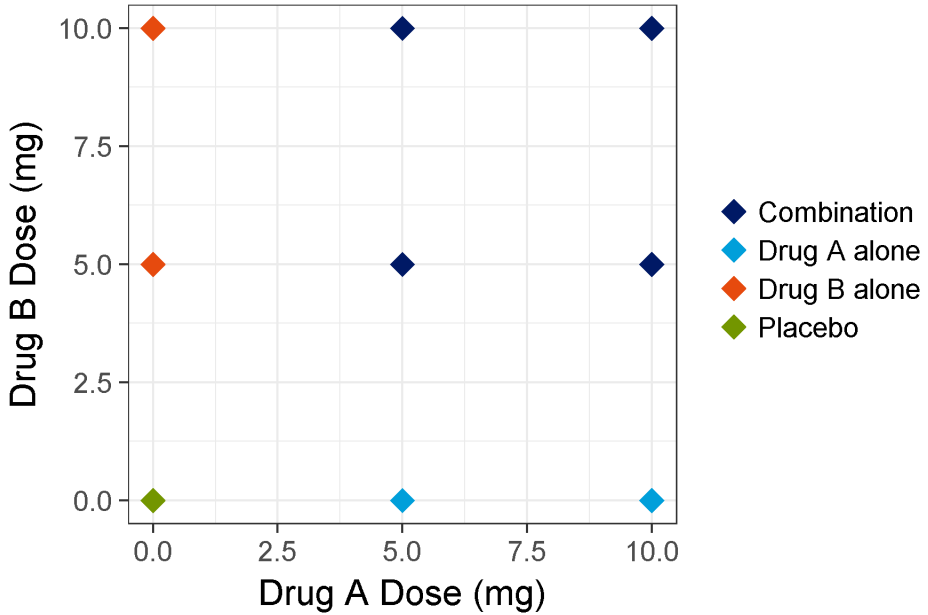
Methods

Design optimizations

- Design optimizations was performed with respect to dose allocation.
  - Monotherapy and combination doses were allowed to vary.
    - Optimizations initiated from the reference design.
    - Search grid from **0 to 10 mg** with 0.1 mg resolution
    - Maximum combination dose based on safety information from phase I
- Drug A parameters were kept fixed
  - Most common situation in clinical drug development for drug combinations[1]
- E_0 assumed to be of little interest
  - Ds optimization family
- PopED was used for the evaluation and optimization of all designs[2]



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2. Nyberg J, Ueckert S, Strömberg EA, Hennig S, Karlsson MO, Hooker AC. PopED: an extended, parallelized, nonlinear mixed effects models optimal design tool. Comput Methods Programs Biomed. 2012;108(2):789-805.

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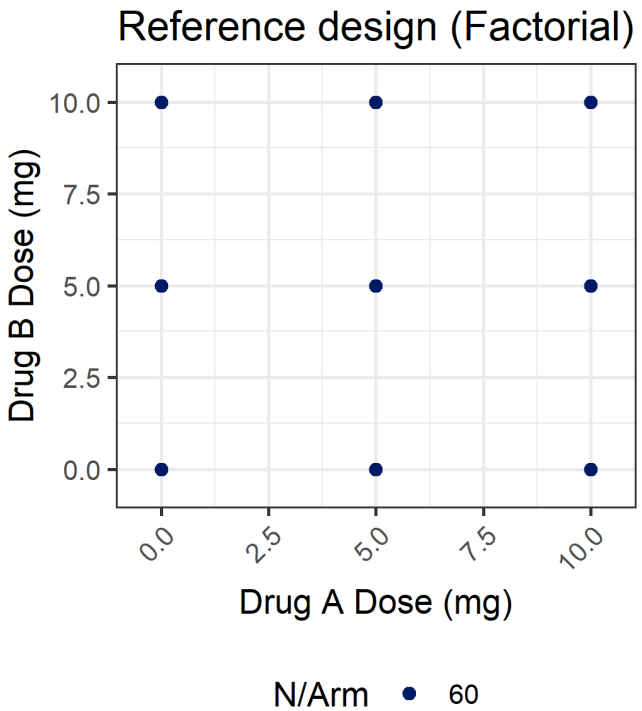
Results

Reference design (3x3 factorial)

- Evaluation of reference design
  - Low expected overall parameter precision[1]
  - Very little information on $EC_{50,B}$ and the interaction parameter α

Parameter Precision (RSE (%))

Parameter	Value	Factorial
E_0 (%)	3	14.9
$E_{max,B}$ (%)	4.5	42.4
$EC_{50,B}$ (ng/mL)	20	95.8
α (unitless)	0.15	50.7
Average RSE (%)	-	51
Ds-Efficiency (%)	-	100



FIM (Fisher Information Matrix) predicted RSEs(%)
N/Arm: Number of subjects per arm

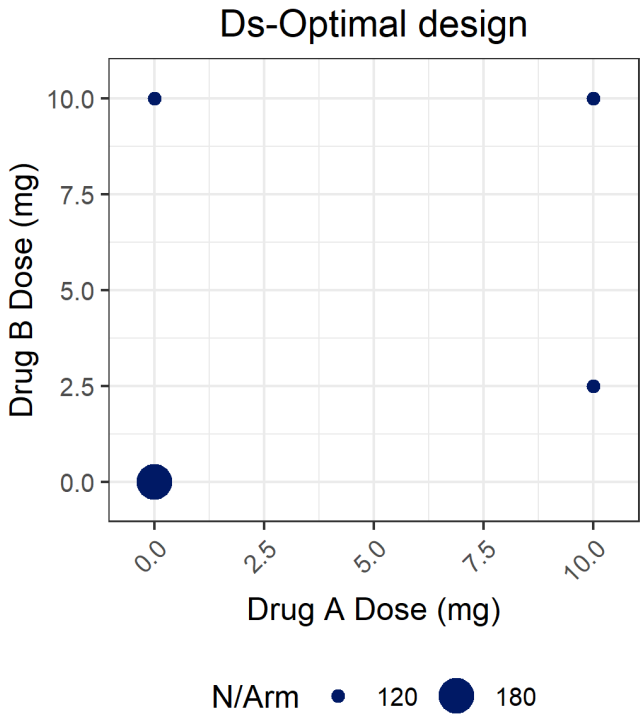
1. Papathanasiou, T., Strathe, A., & Hooker, A. C. (2018). Feasibility of Exposure-Response Analyses for Clinical Dose-Ranging Studies of Drug Combinations

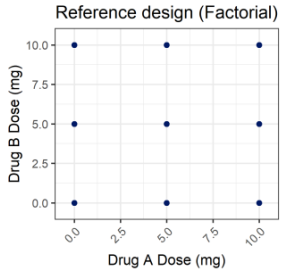
Results

Ds-Optimal design

- 41% gain in Ds-efficiency
  - Same information content with reference with as little as **324** subjects
- Simpler than reference design
  - Four arms were shown to be adequate for parameter estimation

		Parameter Precision (RSE (%))		
Parameter	**Value**	**Factorial**		**Ds-Optimal**
E_0 (%)	3	14.9	▬	14.9
$E_{max,B}$ (%)	4.5	42.4	▲	28.1
$EC_{50,B}$ (ng/mL)	20	95.8	▲	66.8
α (unitless)	0.15	50.7	▲	45.2
Average RSE (%)	-	51	▲	38.8
Ds-Efficiency (%)	-	100	▲	141.2





FIM (Fisher Information Matrix) predicted RSEs(%)
N/Arm: Number of subjects per arm
Same weights across trials (i.e. N/arm) for all doses: N = 60/arm. Some arms are replicates

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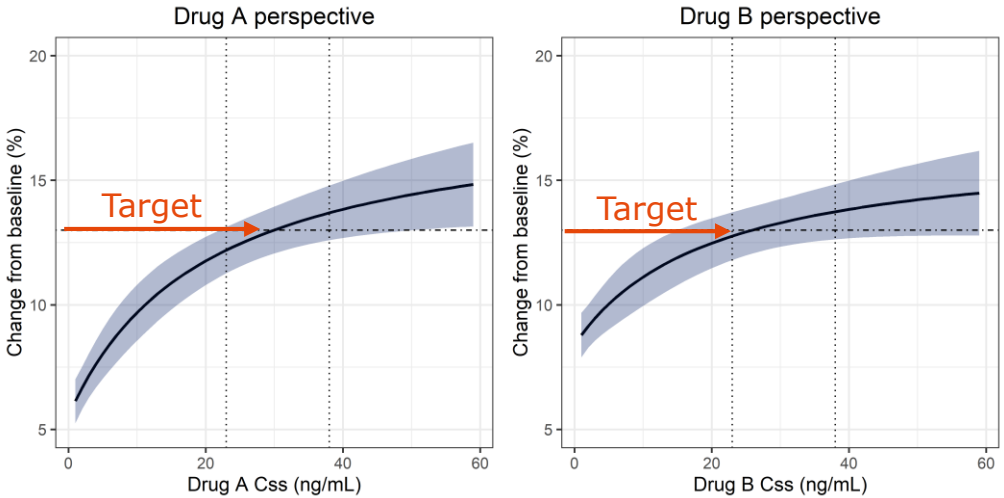
Results

Ds-Optimal design – model predictions

- Performing clinical trials simply to obtain accurate parameters estimates is somewhat implausible
- Dose-finding trials objective
  - Maximize the confidence of dose-selection for confirmatory trials
  - Minimize the prediction variance around a desired (pre-specified) effect level
- D-optimal designs
  - Maximize information in the parameter space
  - Potentially suboptimal for predictions at a desired effect level

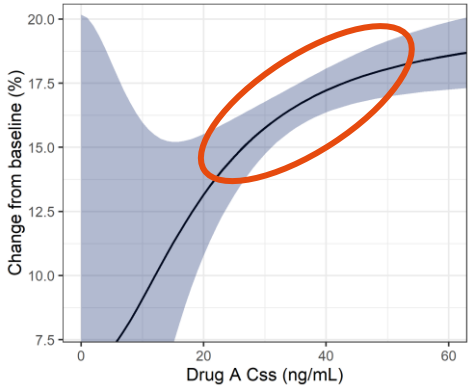


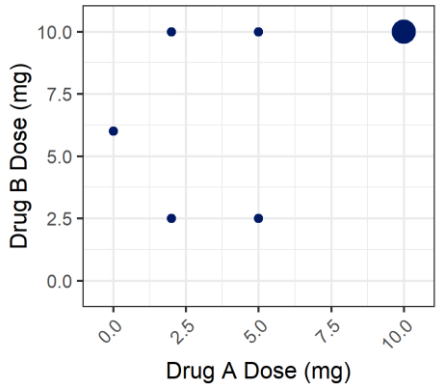
Results

Compound Ds/V-Optimal design

- V-Optimal designs
  - Focus on minimizing the model prediction variance over a range of concentration of drug A and drug B[1]
- **Advantages**
  - Very good prediction for a wanted area of the E-R curve
- **Disadvantages**
  - Very imprecise parameter estimates (expected)[1]
  - Implausible clinical trial design
- **Solution**: A combination of Ds and V
  - Equal contribution of Ds- and V-optimality criteria

$$Ds/V(\xi) = \kappa \cdot log\ Eff_{Ds}(\xi) + (1-\kappa) \cdot log\ Eff_{V}(\xi)$$





ξ: Design variable
Eff_D: D-efficiency
Eff_V: V-efficiency
κ: integer ($0 \leq \kappa \leq 1$)
Controls how much each design criterion influences the final design

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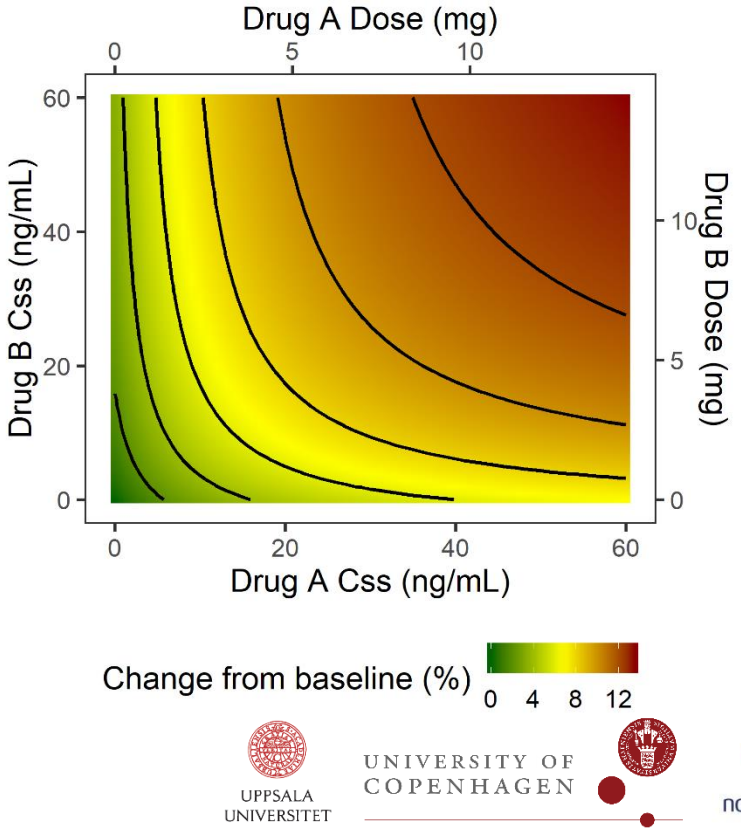
1. Miller F, Guilbaud O, Dette H. Optimal designs for estimating the interesting part of a dose-effect curve. J Biopharm Stat. 2007;17(6):1097-115

Results

Scenario for correct dose identification



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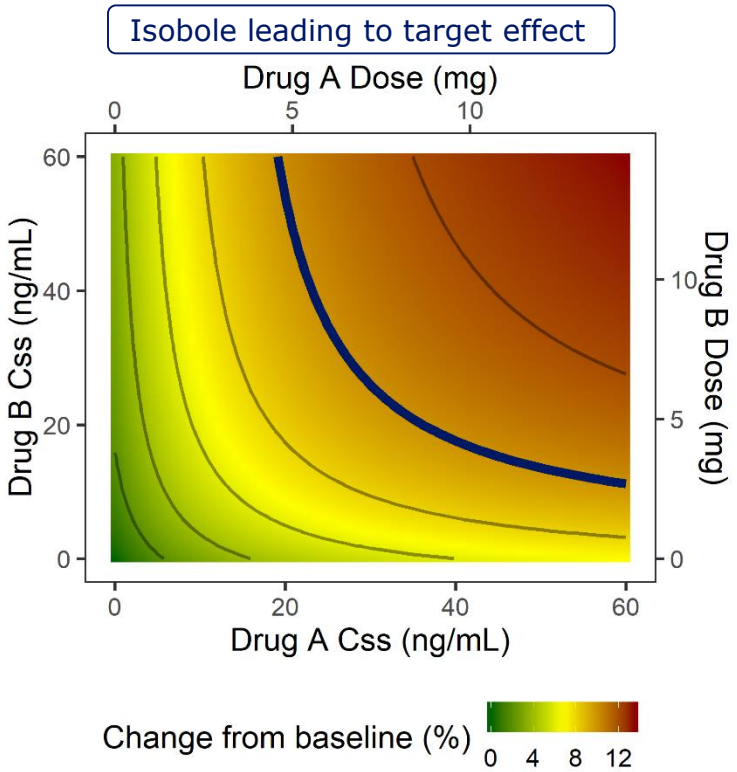
Results

Scenario for correct dose identification

- Target effect: Δ_{Target} = 10%
  - 3% CFB for placebo
  - Dark blue line represent the true 13% (10%+3%) isobole



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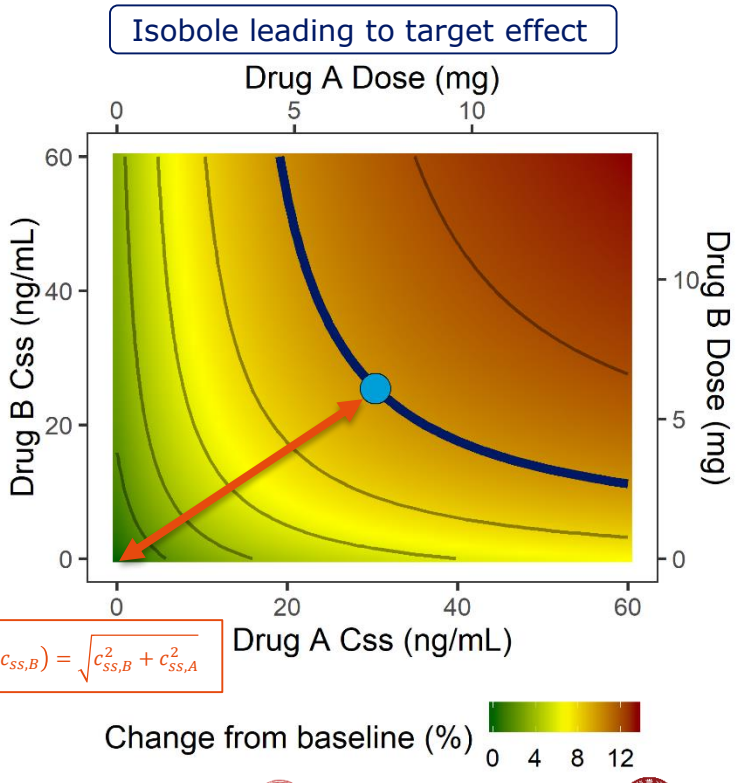
Results

Scenario for correct dose identification

- Target effect: Δ_{Target} = 10%
  - 3% CFB for placebo
  - Dark blue line represent the true 13% (10%+3%) isobole
- Optimal dose-combination for target effect
  - Light blue dot: the smallest combination of both drugs leading to the target effect

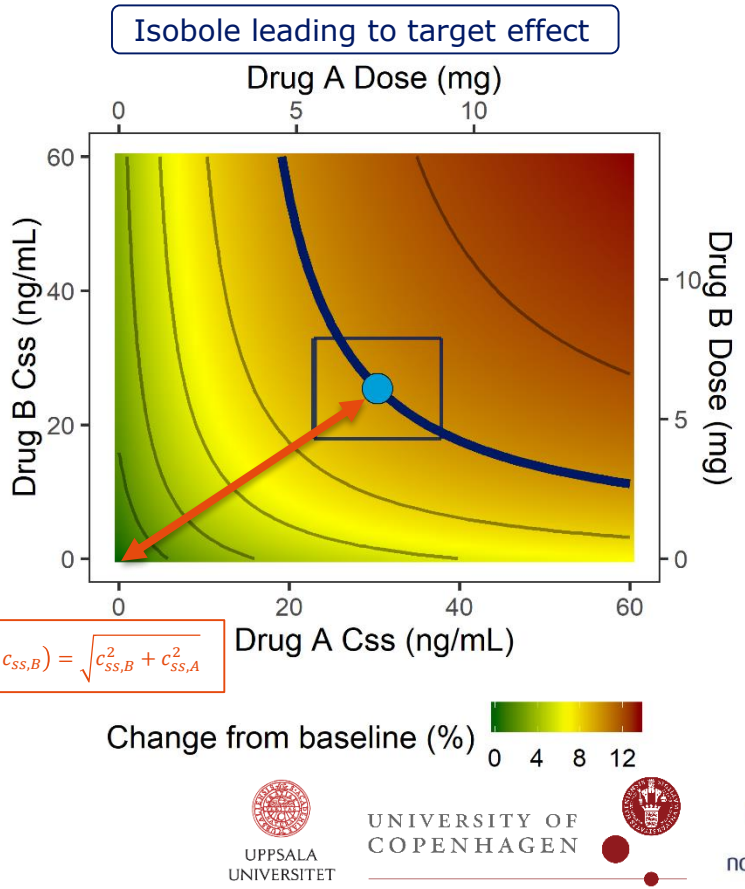


$MEC_{A,B}$: Combined minimum effective concentration

Results

Scenario for correct dose identification

- Target effect: Δ_{Target} = 10%
  - 3% CFB for placebo
  - Dark blue line represent the true 13% (10%+3%) isobole
- Optimal dose-combination for target effect
  - Light blue dot: the smallest combination of both drugs leading to the target effect
- Square represents the area over which the integration for the Ds/V-Optimality criterion was performed
  - Square around the optimal dose-combination with a length of each side L=15 ng/mL (chosen arbitrarily)



$MEC_{A,B}$: Combined minimum effective concentration

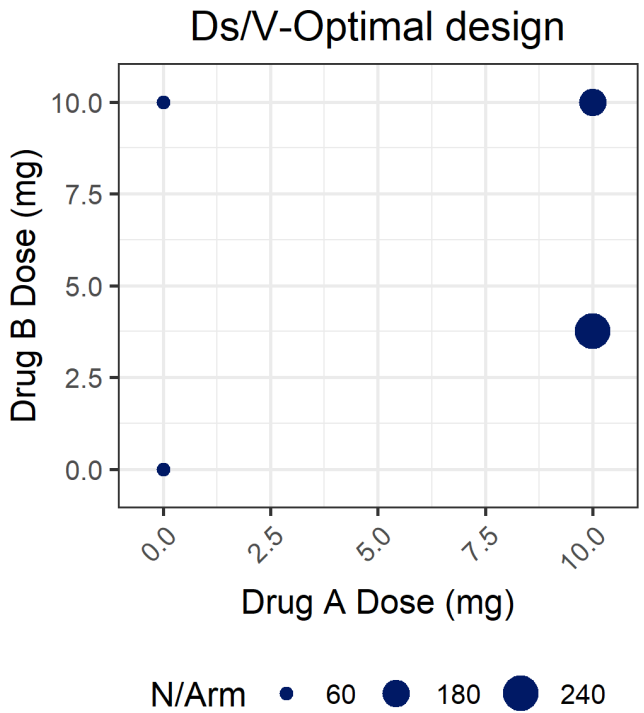
Results

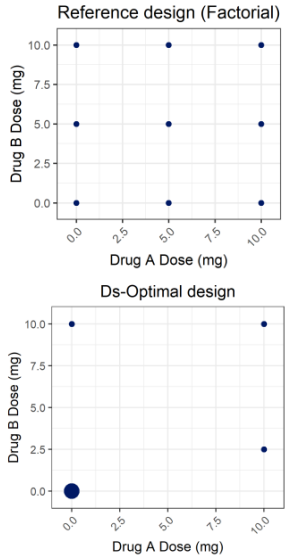
Compound Ds/V-Optimal design

- Ds-efficiency
  - Some loss when compared to the Ds-optimal design
  - More Ds-efficient than the reference design
- Dose allocation
  - Four arms were shown to be adequate
  - Less clustering around placebo

Parameter Precision (RSE (%))

Parameter	Value	Factorial	Ds-Optimal	Ds/V-Optimal
E_0 (%)	3	14.9	14.9	25.8
$E_{max,B}$ (%)	4.5	42.4	28.1	34
$EC_{50,B}$ (ng/mL)	20	95.8	66.8	60.8
α (unitless)	0.15	50.7	45.2	61.4
Average RSE (%)	-	51	38.8	45.5
Ds-Efficiency (%)	-	100	141.2	107.5





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N/Arm: Number of subjects per arm
Same weights across trials (i.e. N/arm) for all doses: N = 60/arm. Some arms are replicates

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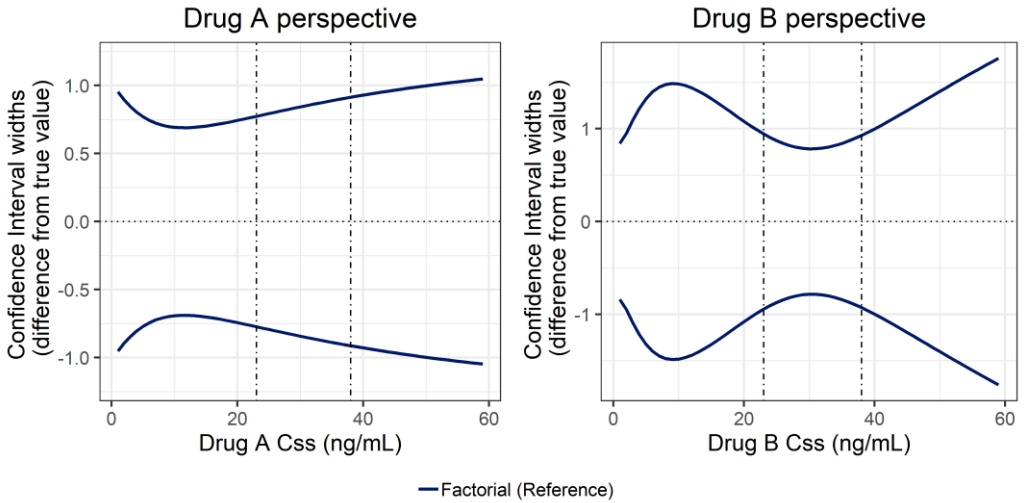
Results

Surface 95% Confidence Intervals around target effect

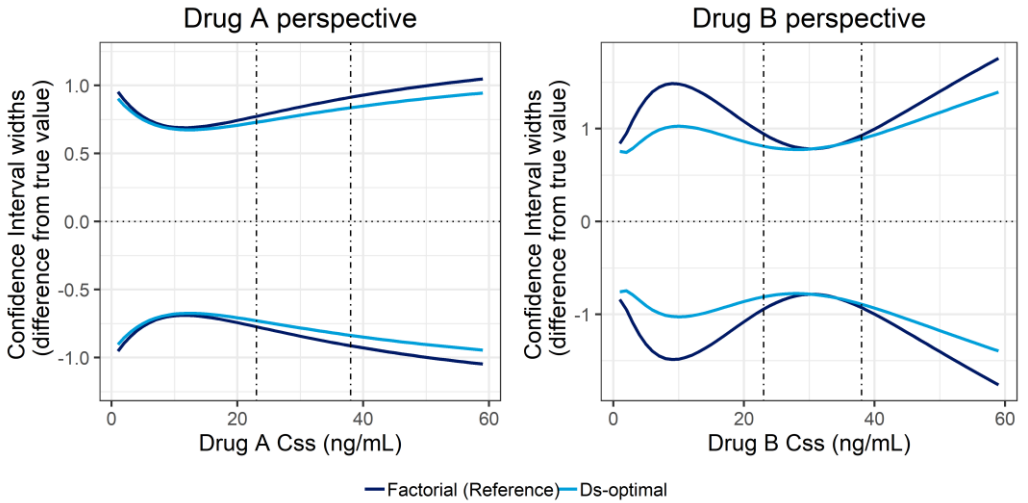


Model 95% CIs calculation was based on the Delta method

Results

Surface 95% Confidence Intervals around target effect

- Little gain in prediction certainty for the Ds-optimal design

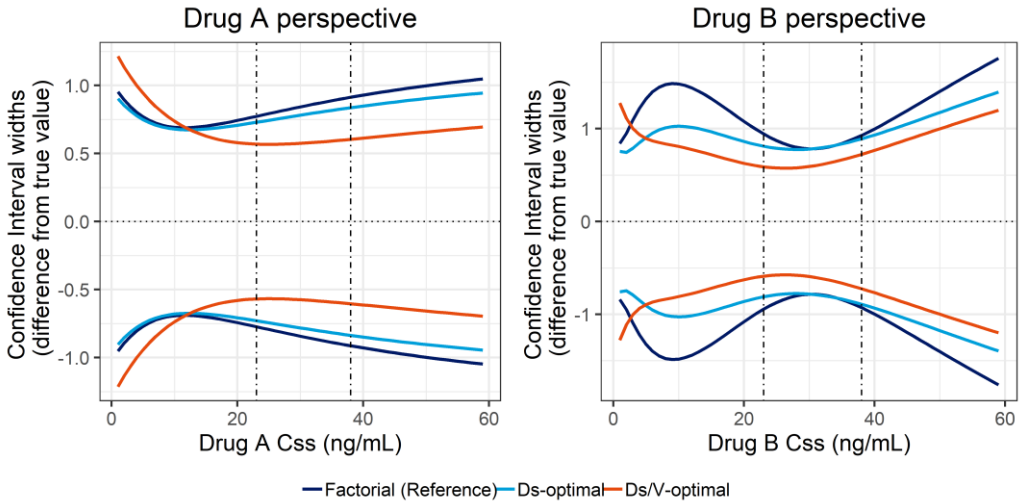


Model 95% CIs calculation was based on the Delta method

Results

Surface 95% Confidence Intervals around target effect

- Little gain in prediction certainty for the Ds-optimal design
- Ds/V-optimal design lead to the highest prediction certainty around the target effect



Model 95% CIs calculation was based on the Delta method

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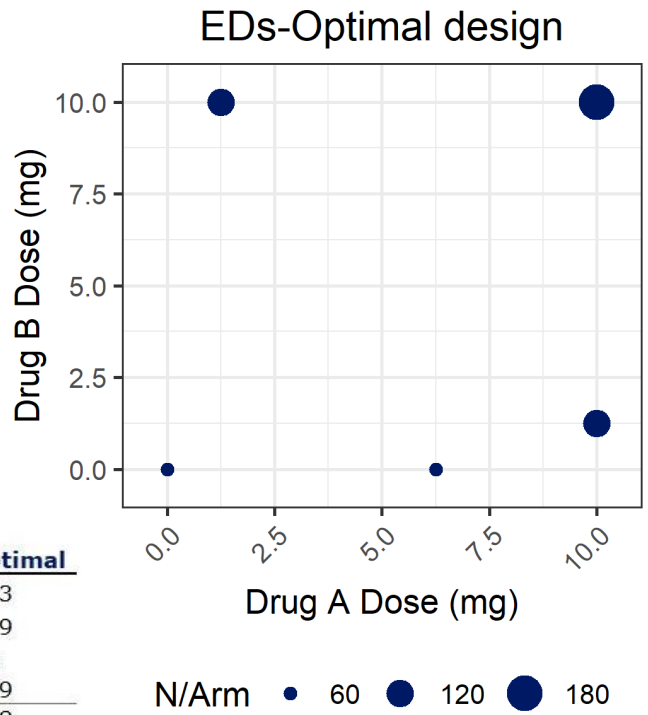
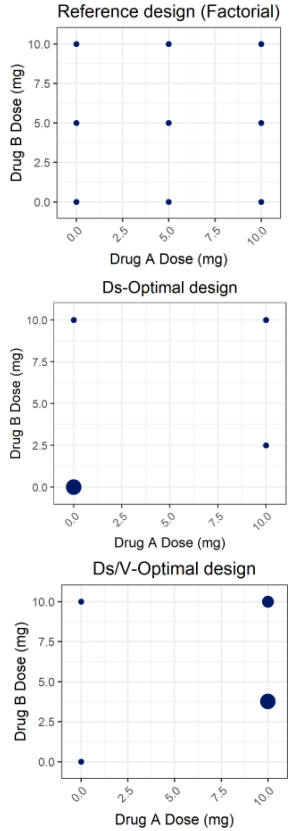
Results

EDs-optimal design

- For nonlinear models, designs are optimal only for the evaluated parameter vector[1]
  - Design with uncertainty in parameter space
    - Uncertainty around **all** parameters
- Similar efficiency as compared to the reference
  - More generalizable design
  - Fewer arms as compared to the reference





Parameter Precision (RSE (%))

Parameter	Value	Distribution	Factorial	Ds-Optimal	EDs-Optimal
E_0 (%)	3	U(2.5, 3.5)	14.9	14.9	18.3
$E_{max,B}$ (%)	4.5	U(3, 9)	42.4	28.1	33.9
$EC_{50,B}$ (ng/mL)	20	U(5, 35)	95.8	66.8	82
α (unitless)	0.15	U(-0.075, 0.175)	50.7	45.2	64.9
Average RSE (%)	-		51	38.8	49.8
Ds-Efficiency (%)	-		100	141.2	98.7

FIM (Fisher Information Matrix) predicted RSEs(%)
N/Arm: Number of subjects per arm
Same weights across trials (i.e. N/arm) for all doses: N = 60/arm. Some arms are replicates

1. Dodds et al., Robust Population Pharmacokinetic Experiment Design. Journal of Pharmacokinetics and Pharmacodynamics, 2005.

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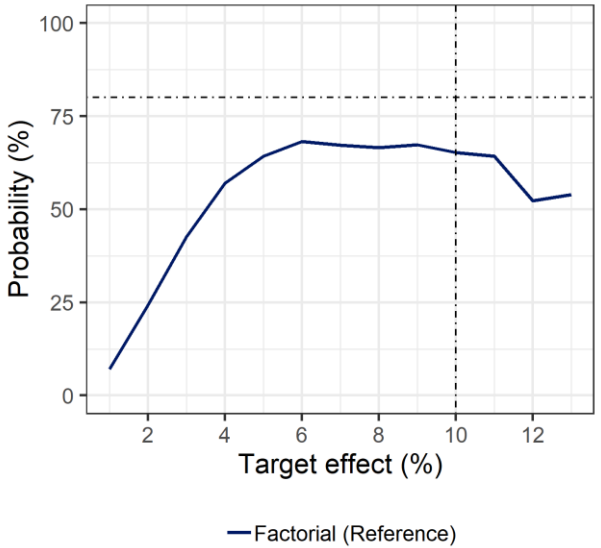
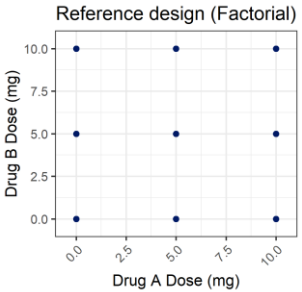
Results

Probabilities for correct dose identification

- Stochastic Simulation and Estimation (SSE) was performed based on the reference and optimized designs
  - 1000 SSE replicates
  - Probabilities that the estimated combination doses are within 20% of the true ones





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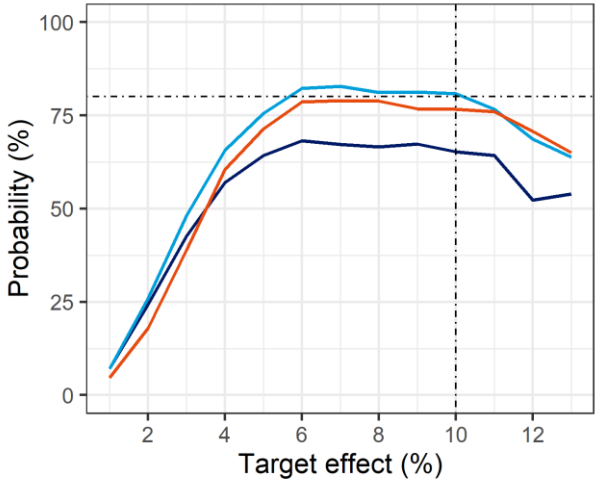

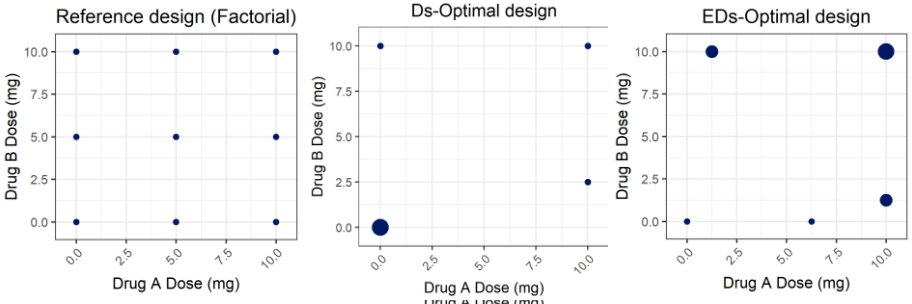

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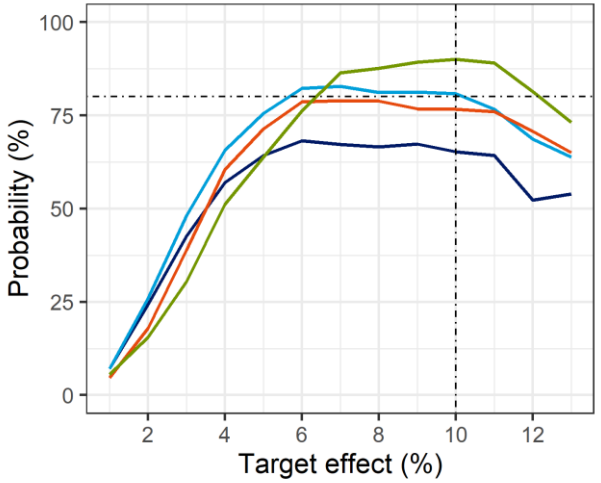
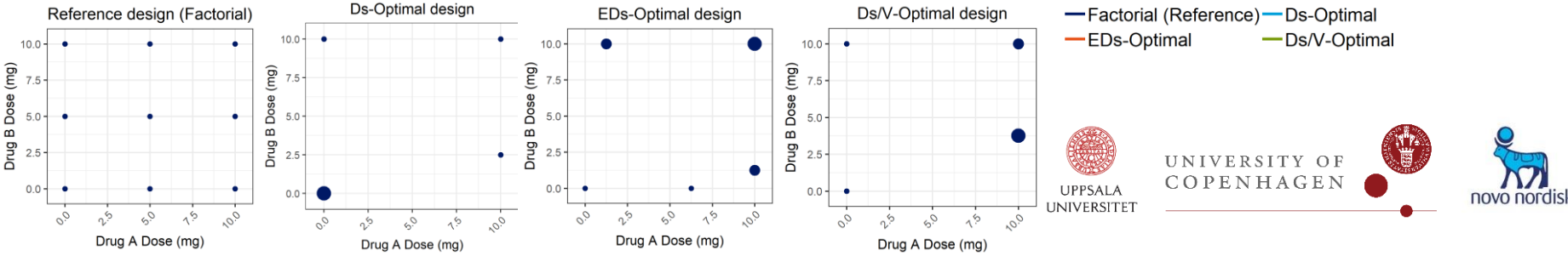
- Best performance is seen using the Ds/V design





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Conclusions and perspectives

- Optimized studies
  - Significantly improved the extracted amount of information
  - Allowed for higher confidence in decision making
  - Required smaller number of arms
- Compound D/V-criterion designs are a promising way forward for dose finding in combination therapy studies
- Future research should focus on
  - Expanding the methodology to include safety signals
  - Exploring the influence of uncertainty in the combination model structure

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- The Pharmacometrics group, University of Copenhagen
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