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

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\textsuperscript{1,2}
- Poor dose selection is still an important cause of the high attrition rate in confirmatory trials\textsuperscript{1,2}
- Accurate delineation of the Dose–Exposure–Response (DER) relationship is a key aspect for rational dose selection\textsuperscript{1,2}

\begin{itemize}
\item Background Dose selection in clinical drug development
\end{itemize}

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

\[
C_{ss,x}(\text{Dose}_x) = \frac{\text{Dose}_x \cdot F_x}{CL_{x,i} \cdot \tau} \quad CL_{x,i} = \theta_x e^{\eta_{x,i}} \quad \eta_{x,i} \sim N(0, \omega_x^2)
\]

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

\[ E = E_0 \]

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Combination Dose-Exposure-Response model

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Methods

Combination Dose-Exposure-Response model

\[ E_A = \frac{E_{\text{max},A} \cdot C_{SS,A}^{\gamma_A}}{E_{C50,A}^{\gamma_A} + C_{SS,A}^{\gamma_A}} \]

\[ E_B = \frac{E_{\text{max},B} \cdot C_{SS,B}^{\gamma_B}}{E_{C50,B}^{\gamma_B} + C_{SS,B}^{\gamma_B}} \]

\[ E = E_0 + E_A + E_B \]

Methods

Combination Dose-Exposure-Response model

\[
E_A = \frac{E_{\text{Max}, A} \cdot C_{\text{SS}, A}^{\gamma A}}{E_{C_{50}, A}^{\gamma A} + C_{\text{SS}, A}^{\gamma A}}
\]

\[
E_B = \frac{E_{\text{max}, B} \cdot C_{\text{SS}, B}^{\gamma B}}{E_{C_{50}, B}^{\gamma B} + C_{\text{SS}, B}^{\gamma B}}
\]

\[
E = E_0 + E_A + E_B + \alpha E_A E_B + \varepsilon, \quad \varepsilon \sim N(0, \sigma^2)
\]

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

Methods

Combination Dose-Exposure-Response model

\[ E_A = \frac{E_{\text{Max},A} \cdot C_{\text{SS},A}^{\gamma_A}}{E_C_{50,A}^{\gamma_A} + C_{ss,A}^{\gamma_A}} \]

\[ E_B = \frac{E_{\text{max},B} \cdot C_{ss,B}^{\gamma_B}}{E_C_{50,B}^{\gamma_B} + C_{ss,B}^{\gamma_B}} \]

\[ E = E_0 + E_A + E_B + \alpha E_A E_B + \epsilon, \quad \epsilon \sim N(0, \sigma^2) \]

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

\[ a = 0.15 \]

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
- \(N_{\text{trial}} = 540\) 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 \(\Delta = 5\%\) from placebo

Level of variance: 6% sd. 95% power. 95% significance level of \(\alpha = 0.05\)

**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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Results

Reference design (3x3 factorial)

- Evaluation of reference design
  - Low expected overall parameter precision
  - Very little information on EC$_{50,B}$ and the interaction parameter $\alpha$

<table>
<thead>
<tr>
<th>Parameter Precision (RSE (%))</th>
<th>Value</th>
<th>Factorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_0$ (%)</td>
<td>3</td>
<td>14.9</td>
</tr>
<tr>
<td>$E_{max,B}$ (%)</td>
<td>4.5</td>
<td>42.4</td>
</tr>
<tr>
<td>EC$_{50,B}$ (ng/mL)</td>
<td>20</td>
<td>95.8</td>
</tr>
<tr>
<td>$\alpha$ (unitless)</td>
<td>0.15</td>
<td>50.7</td>
</tr>
<tr>
<td>Average RSE (%)</td>
<td>-</td>
<td>51</td>
</tr>
<tr>
<td>Ds-Efficiency (%)</td>
<td>-</td>
<td>100</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Factorial</th>
<th>Ds-Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>E₀ (%)</td>
<td>3</td>
<td>14.9</td>
<td>14.9</td>
</tr>
<tr>
<td>Eₘₙ₅₋₅0 (%)</td>
<td>4.5</td>
<td>42.4</td>
<td>28.1</td>
</tr>
<tr>
<td>EC₅₀,₅0 (ng/mL)</td>
<td>20</td>
<td>95.8</td>
<td>66.8</td>
</tr>
<tr>
<td>α (unitless)</td>
<td>0.15</td>
<td>50.7</td>
<td>45.2</td>
</tr>
<tr>
<td>Average RSE (%)</td>
<td>-</td>
<td>51</td>
<td>36.8</td>
</tr>
<tr>
<td>Ds-Efficiency (%)</td>
<td>-</td>
<td>100</td>
<td>141.2</td>
</tr>
</tbody>
</table>

FIM (Fisher Information Matrix) predicted RSEs(%)
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
Ds-Optimal design – model predictions
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

- **Advantages**
  - Very good prediction for a wanted area of the E-R curve

- **Disadvantages**
  - Very imprecise parameter estimates (expected)
  - Implausible clinical trial design

- **Solution**: A combination of Ds and V
  - Equal contribution of Ds- and V-optimality criteria

\[
Ds/V(\xi) = \kappa \cdot \log \text{Eff}_{Ds}(\xi) + (1 - \kappa) \cdot \log \text{Eff}_{V}(\xi)
\]

\(\xi\): Design variable
\(\text{Eff}_D\): D-efficiency
\(\text{Eff}_V\): V-efficiency
\(\kappa\): integer \((0 \leq \kappa \leq 1)\)

Controls how much each design criterion influences the final design

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Results

Scenario for correct dose identification
**Results**

**Scenario for correct dose identification**

- Target effect: $\Delta_{\text{Target}} = 10$
  - 3% CFB for placebo
  - Dark blue line represent the true 13% (10%+3%) isobole
**Results**

**Scenario for correct dose identification**

- **Target effect:** $\Delta_{\text{Target}} = 10\%$
  - 3% CFB for placebo
  - Dark blue line represents 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

\[
\text{MEC}_{A,B} = \sqrt{c_{ss,B}^2 + c_{ss,A}^2}
\]
**Results**

**Scenario for correct dose identification**

- **Target effect**: $\Delta_{\text{Target}} = 10\%$
  - 3% CFB for placebo
  - Dark blue line represents 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)

**Isobole leading to target effect**

$$M_{\text{EC}}(c_{ss,A}, c_{ss,B}) = \sqrt{c_{ss,B}^2 + c_{ss,A}^2}$$

$M_{\text{EC}}_{A,B}$: 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 (%))

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Factorial</th>
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<th>Ds/V-Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$E_0$ (%)</td>
<td>3</td>
<td>14.9</td>
<td>14.9</td>
<td>25.8</td>
</tr>
<tr>
<td>$E_{max,0}$ (%)</td>
<td>4.5</td>
<td>42.4</td>
<td>28.1</td>
<td>34</td>
</tr>
<tr>
<td>$EC_{50,B}$ (ng/mL)</td>
<td>20</td>
<td>95.8</td>
<td>66.8</td>
<td>60.8</td>
</tr>
<tr>
<td>$q$ (unitless)</td>
<td>0.15</td>
<td>50.7</td>
<td>45.2</td>
<td>61.4</td>
</tr>
<tr>
<td>Average RSE (%)</td>
<td>-</td>
<td>51</td>
<td>38.8</td>
<td>45.5</td>
</tr>
<tr>
<td>Ds-Efficiency (%)</td>
<td>-</td>
<td>100</td>
<td>141.2</td>
<td><strong>107.5</strong></td>
</tr>
</tbody>
</table>

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.
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
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

### Results

**EDs-Optimal design**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Distribution</th>
<th>Factorial</th>
<th>Ds-Optimal</th>
<th>EDs-Optimal</th>
</tr>
</thead>
<tbody>
<tr>
<td>( E_0 (%) )</td>
<td>3</td>
<td>U(2.5, 3.5)</td>
<td>14.9</td>
<td>14.9</td>
<td>18.3</td>
</tr>
<tr>
<td>( E_{max,B} (%) )</td>
<td>4.5</td>
<td>U(3, 9)</td>
<td>42.4</td>
<td>28.1</td>
<td>33.9</td>
</tr>
<tr>
<td>( EC_{50,B} (ng/mL) )</td>
<td>20</td>
<td>U(5, 35)</td>
<td>95.8</td>
<td>66.8</td>
<td>82</td>
</tr>
<tr>
<td>( a ) (unitless)</td>
<td>0.15</td>
<td>U(-0.075, 0.175)</td>
<td>50.7</td>
<td>45.2</td>
<td>64.9</td>
</tr>
</tbody>
</table>

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

---

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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  - 1000 SSE replicates
  - Probabilities that the estimated combination doses are within 20% of the true ones
- Optimized designs consistently led to higher probability of correct dose-identification
- Best performance is seen using the Ds/V design
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
Acknowledgements

- The Pharmacometrics Group, Uppsala University
- The Pharmacometrics group, University of Copenhagen
- Quantitative Clinical Pharmacology, Novo Nordisk A/S
- This work was supported by the Innovation Foundation Denmark