PODE 2008

Optimization of sampling times for a combined PK/PD model: optimal design as a reference point

Sergei Leonov
(Research Statistics Unit, GSK)

Joint work with Mindy Magee and Brian McHugh (CPK M&S, GSK)

Paris, June 23
Outline

- Background: clinical problem
- Original sampling design
- Optimization of sampling times
- Comparison options
Endpoints

- Safety
- Efficacy
- PK
- PK/PD

Study Design

Endpoints

- Safety
- Efficacy
- PK
- PK/PD
Final PK/PD Model

\[ E = E_0 \cdot \left(1 - \frac{C_p}{IC_{50} + C_p}\right) \]

\[ V/F \]

\[ CL/F \]

\[ k_a \]

- \( k_a \): first-order absorption rate constant (h\(^{-1}\))
- \( V/F \): apparent volume of distribution (L)
- \( CL/F \): apparent systemic clearance (L/h)
- \( E_0 \): PD endpoint at baseline (nM/min/mL)
- \( IC_{50} \): Drug X plasma concentration causing 50% inhibition of PD endpoint (ng/mL)
# Final PK/PD Sampling Scheme

<table>
<thead>
<tr>
<th>Sample Collection Timepoint</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-dose (Trough concentration)</td>
<td>Baseline / Randomization</td>
</tr>
<tr>
<td>0.5-5 hours after dose (Absorption phase)</td>
<td>X</td>
</tr>
<tr>
<td>5-9 hours after dose (Peak concentration)</td>
<td>X</td>
</tr>
<tr>
<td>9-22 hours after dose (Elimination phase)</td>
<td>X³</td>
</tr>
</tbody>
</table>

1. If the subject is withdrawn early, a blood sample for PK and PD should be collected prior to discharge from the study, if possible.
2. For each PK sample, a PD sample will be drawn at the same time to assess the plasma PD endpoint.
3. Subjects should be reminded to take their study medication around lunch time for the 2 days prior to clinic visit.

4 samples to be selected
- Week 4, between [0.5, 5] h
- Week 6, between [9, 22] h
- Week 8, between [0.5, 5] h
- Week 10, between [5, 9] h

Forced samples:
- PD trough (0 h)
- Trough PK/PD, weeks 4 and 8
Main goal: validate proposed design

- 4 “flexible” candidate times
- Given frequency e.g. every 30 min
  1. Day 4, [0.5, 5] h: 10 points
  2. Day 6, [0.5, 5] h: 10 points
  3. Day 6, [5, 9] h: 9 points
  4. Day 6, [9, 22] h: 17 points

PK/PD curves

Doses: loading 250 mg, maintenance 250 mg, every 24 h

PD response

Time (hours)
Nonlinear models, multiple responses

- Predictor $\mathbf{x} = (x_1, x_2, \ldots, x_k)$ - sequence of sampling times,
- Measurements $\mathbf{Y} = [y(x_1), \ldots, y(x_k)]$ - vector,
- Response $\eta(\mathbf{x}, \theta) = [\eta(x_1, \theta), \ldots, \eta(x_k, \theta)]$ - vector

Key: $\mu(\mathbf{x}, \theta)$ - information matrix of a $k$-dimensional sequence $\mathbf{x}$
Optimal design

Information matrix: \( n_i \) patients on seq. \( x_i \) \( \implies M_N(\theta) = \sum_{i=1}^{N} n_i \mu(x_i, \theta) \)

Variance of the MLE: \( \text{Var}(\hat{\theta}) \approx M_N^{-1}(\theta) \)

\[
M(\xi, \theta) = \frac{M_N(\theta)}{N} = \sum_i w_i \mu(x_i, \theta) \quad - \text{normalized information, per observation}
\]

\( \xi = \{w_i, x_i\} \) - normalized design; \( w_i = n_i/N \) - weights

\( D(\xi, \theta) = M^{-1}(\xi, \theta) \) - normalized variance-covariance matrix

Restrictions on the number of optimal sequences: NONE
Optimal design (cont.)

Criterion of optimality \( \Psi(\xi, \theta) \rightarrow \min_{\xi} \): minimization with respect to 

- weights \( w_i, 0 \leq w_i \leq 1, \Sigma_i w_i = 1 \)
- admissible sampling sequences \( x_i \in X \) - design region.

Locally optimal designs:

D-criterion: \( \Psi = |D(\xi, \theta)| \); A-criterion: \( \Psi = \text{tr}[AD(\xi, \theta)] \)

Equivalence Theorem: Kiefer, Wolfowitz (1960), Fedorov (1972) - background for algorithms
Information matrix for sequence \( \mathbf{x} \)

Gaussian \( Y : \mathbb{E}[Y | \mathbf{x}] = \eta(\mathbf{x}, \theta), \quad \text{Var}[Y | \mathbf{x}] = S(\mathbf{x}, \theta) \)

\[ \mu(\mathbf{x}, \theta) \text{- information matrix of a single (} k \text{-dimensional) sequence} \mathbf{x}: \]

\[ \mu_{\alpha\beta}(\mathbf{x}, \theta) = \frac{\partial \eta}{\partial \theta_\alpha} S^{-1} \frac{\partial \eta}{\partial \theta_\beta} + \frac{1}{2} \text{tr} \left[ S^{-1} \frac{\partial S}{\partial \theta_\alpha} S^{-1} \frac{\partial S}{\partial \theta_\beta} \right], \]

\[ S = S(\mathbf{x}, \theta), \quad \eta = \eta(\mathbf{x}, \theta) \quad [\text{Muirhead (1982), Magnus and Neudecker (1988)}] \]

If \( \eta, S \) defined (approximated) \( \Rightarrow \) get \( \mu \) \( \Rightarrow \) run the algorithm

Vector \( Y \) combines PK and PD responses
Information matrix for sequence $x$ (cont.)

- **Data** $y(x_{ij}) = \eta(x_{ij}, \gamma_i) \left[ 1 + \varepsilon^p_{ij} \right] + \varepsilon^a_{ij}, \quad j = 1, \ldots, k_i. \quad (1)$

  $\varepsilon^a_{ij} \sim N(0, \sigma_a^2), \quad \varepsilon^p_{ij} \sim N(0, \sigma_p^2)$

First-order approximation of variance matrix $S$, model (1): for normal $\gamma$

$$S(x, \theta) \approx F \Lambda F^T + \sigma_p^2 \ Diag[\eta(x, \theta) \eta^T(x, \theta) + F \Lambda F^T] + \sigma_A^2 I_k,$$

$$F = F(x, \gamma^0) = \frac{\partial \eta(x, \theta)}{\partial \gamma_\alpha} \bigg|_{\gamma=\gamma^0} \quad (k \times m_\gamma) \text{ matrix}$$

Retout, Mentré (2003), Gagnon and Leonov (2005)
Optimal designs: not necessarily practical

\[ \text{Response } r(x, \theta) = \theta_0 + \theta_1 x \]

\[ \text{Allowed: any } x_i \in [0,1] \]

\[ \text{any } n_i, \quad \sum_i n_i = N \]

D-optimal design: N/2 measurements at the ends
Optimal design does not depend on parameter values!
Optimal designs: not necessarily practical

Binary logistic model: \( P(\text{response}|\theta) = \exp(\theta_0+\theta_1x) / [1+ \exp(\theta_0+\theta_1x)] \)

Two optimal doses with equal weights on z-scale: \( z = \theta_0+\theta_1x \)  

\( z^* = \pm 1.54 \) (Logit),  \( z^* = \pm 1.14 \) (Probit)
One-compartment PK and $E_{\text{max}}$ PD

Parameters:
- $K_a$, $V/F$, $CL/F$ (PK)
- $E_{\text{max}}$, $IC_{50}$ (PD)

Candidate sampling times
No PD samples option

No PD samples
Sensitivity function
Efficiency analysis: best and worst sequences

- **BEST SEQUENCES:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Effic.</th>
<th>Wk 2,D4</th>
<th>Wk 2,D6</th>
<th>Wk 2,D6</th>
<th>Wk 2,D6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.000</td>
<td>3.50</td>
<td>3.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>2</td>
<td>0.999</td>
<td>4.50</td>
<td>3.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>3</td>
<td>0.999</td>
<td>3.50</td>
<td>4.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>4</td>
<td>0.998</td>
<td>4.50</td>
<td>4.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>5</td>
<td>0.997</td>
<td>5.00</td>
<td>3.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>6</td>
<td>0.997</td>
<td>3.50</td>
<td>5.00</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>7</td>
<td>0.997</td>
<td>2.50</td>
<td>3.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>8</td>
<td>0.997</td>
<td>3.50</td>
<td>2.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
<tr>
<td>9</td>
<td>0.996</td>
<td>3.50</td>
<td>3.50</td>
<td>6.00</td>
<td>22.00</td>
</tr>
<tr>
<td>10</td>
<td>0.996</td>
<td>5.00</td>
<td>4.50</td>
<td>5.00</td>
<td>22.00</td>
</tr>
</tbody>
</table>

- **WORST SEQUENCES:**

<table>
<thead>
<tr>
<th>No.</th>
<th>Effic.</th>
<th>Wk 2,D4</th>
<th>Wk 2,D6</th>
<th>Wk 2,D6</th>
<th>Wk 2,D6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.817</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>17.00</td>
</tr>
<tr>
<td>2</td>
<td>0.818</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>16.00</td>
</tr>
<tr>
<td>3</td>
<td>0.819</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>18.00</td>
</tr>
<tr>
<td>4</td>
<td>0.820</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>15.00</td>
</tr>
<tr>
<td>5</td>
<td>0.822</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>19.00</td>
</tr>
<tr>
<td>6</td>
<td>0.824</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>14.00</td>
</tr>
<tr>
<td>7</td>
<td>0.826</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>20.00</td>
</tr>
<tr>
<td>8</td>
<td>0.829</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>13.00</td>
</tr>
<tr>
<td>9</td>
<td>0.831</td>
<td>0.50</td>
<td>0.50</td>
<td>9.00</td>
<td>21.00</td>
</tr>
<tr>
<td>10</td>
<td>0.833</td>
<td>0.50</td>
<td>0.50</td>
<td>8.00</td>
<td>17.00</td>
</tr>
</tbody>
</table>

**EFFICIENCY OF INDIVIDUAL SEQUENCES:** mean 0.950, median 0.956

**EFFICIENCY OF AVERAGE DESIGN** 0.952
Sensitivity analysis

- Comparison with "average" design within sampling windows
  - Currently 5 times are selected uniformly in each sampling window (average value across $5^4 = 625$ sequences)

- Comparison with "average" design within Delta-vicinity of D-optimal designs
  - D-optimal times +/- Delta
Conclusions

- Original design: quite efficient
- Optimal design: used as a reference point
  - Serial dilution (bioassays)
  - Dose response modeling (linear, binary logistic models)
References