Incorporating pharmacokinetic information in phase I studies in small populations
Innovative methodology for small populations research

The focus is on the development of novel methods for the design and analysis of clinical trials in rare diseases or small populations defined, for example, by a rare genetic marker.

Project coordinator: Nigel Stallard

Project funded by: 

February 2014 – May 2017
AIM
To develop novel methodology for improving dose-finding in early phase clinical trials by incorporating data on pharmacokinetics (PK), and pharmacodynamics (PD).

First year: our aim was to propose, to study and to compare methods that use PK measures in the dose-finding designs
How can we incorporate PK?
- Covariate?
- Dependent variable?
Clinical context and work done

Phase I dose-finding clinical Trials

- Objective:
  → estimation of the Maximum Tolerated Dose (MTD)

- Context:
  → discrete and fixed dose levels
  → binary criteria
  → very small sample size
  → adaptive design

- Issues in small samples - rare diseases, pediatrics...

We studied and compared dose-finding methods that use the PK measure in the dose-finding design either as covariate or dependent variable in the dose-finding model.
find existing approaches
(built for specific cases)

modify/adjust them

apply them on the same clinical setting

Comparisons
The idea of introducing PK data in dose escalation studies is not new, but rarely used in practice:

- Collins et al. (1990): Pharmacologically guided phase I trials
- Piantadosi & Liu (1996): parametric dose-response function with a PK measure of exposure as covariate
- Patterson et al. (1999): Bayesian procedure with a nested hierarchical structure
- O’Quigley et al. (2010): dose associated with a mean PK response, based on linear regression
- Patan & Bogacka (2011 DAEW03): Dose selection incorporating PK/PD information in early phase clinical trials
find existing approaches
(built for specific cases)

Google

modify/adjust them

apply them on the same clinical setting

Comparisons
Models modification

Piantadosi and Liu (1996) / PKCOV

- first paper found in literature
- extension of Continual Reassessment Method (CRM)
- parametric dose-response function with quantitative effects for both dose of drug and PK exposure (AUC – area under the curve)

\[
\text{logit}(p_T) = -\beta_0 + \beta_1 d + \beta_2 \Delta_{\text{AUC}}
\]

\[
\text{logit}\left[p_T(d_k, \Delta d_k, \beta)\right] = -\beta_0 + \beta_1 \log d_k + \beta_2 \Delta d_k
\]

Priors:

- \(\beta_2 \sim U(l_2, m_2)\)
- \(\beta_0 \) fixed

Dose allocation rule:

- \(d_{k+1} = \arg\min_{d_k} | p_T(d_k, 0, \beta) - \theta|\)
PK/PD driven dose-selection (1)

Patterson et al. (1999)/PKLIM

- Bayesian procedure with nested hierarchical structure
- mixed-effect model used to analyze the PK data
- choice of the dose: highest dose satisfying constraint or D-optimal
- Cross-over study and healthy volunteers

\[ z_{ij} \mid s_i, \theta, \nu \sim N \left( \theta_1 + \theta_2 \log d_{ij} + s_i, \nu^{-1} \right) \]
\[ s_i \mid \theta, \nu \sim N \left( 0, \rho / (\nu (1 - \rho)) \right) \]
\[ \theta \mid \nu \sim N_2 \left( \mathbf{m}, (\nu \mathbf{Q})^{-1} \right) \]
\[ \nu \sim GA \left( \alpha, \beta \right) \]
PK/PD driven dose-selection (2)

Whitehead et al. (2007)/PKLOG

- simultaneous monitoring of PK and PD responses and of the incidence of adverse events
- three models: dose-PK endpoint (a linear model), PK-PD (quadratic model), PK-toxicity (DLT, logistic model)
- Cross-over study and healthy volunteers

\[
\begin{align*}
    z_{ij} &= \beta (\log(d_{ij} + 1)) + s_i + \epsilon_{ij} \\
    m_{ij} &= \theta_0 + \theta_1 z_{ij} + \theta_3 z_{ij}^2 + r_i + \delta_{ij} \\
    \text{logit}(p_{T,ij}) &= \lambda_1 + \lambda_2 z_{ij}
\end{align*}
\]

\[
P_{i+1} = \arg\min_{d_i} |P(y_{i+1} = 1 | \beta) - \theta|
\]

\[
= \int \frac{1}{1 + \exp(\beta_3 - \beta_4 z)} g(z) dz
\]
Other modifications

\[
\text{CRMPK} = \text{CRM} + \text{PKLM}
\]

Dose allocation rule:

\[
d_{t+1} = \min(d_{\text{cen}}, d_{\text{actmin}})
\]

\[
\text{PKPOP} = \text{PKLOG}
\]

with

\[
d_{t+1} = \arg\min_{d_k} |\hat{p}_t(z_k | \hat{\beta}_k) - \hat{\theta}| \\
\text{mean value predicted}
\]
find existing approaches (built for specific cases)

modify/adjust them

apply them on the same clinical setting

Comparisons
Defining a therapeutic window for the novel TGF-β inhibitor LY2157299 monohydrate based on a pharmacokinetic/pharmacodynamic model

Ivelina Gueorguieva,1 Ann L. Cleverly,1 Anja Stauber,2 N. Sada Pillay,2 Jordi A. Rodon,3 Colin P. Miles,1 Jonathan M. Yingling2 & Michael M. Lahn2

Simulations studies – choosing a PK model

- TGF-β signaling has been recognized as an important regulator of tumor growth
- Inhibiting TGF-β signaling is a novel approach
- They investigated several inhibitors and selected LY2157299

Simulation from preclinical data to predict therapeutic dose range

Clinical trial design depending also on preclinical late toxicity

PK/PD estimation in humans:

- First order absorption linear two compartment model
- Indirect model to relate plasma concentrations of LY2157299 and pSMAD data
Simulations studies – choosing a PK model (2)

Human 360mg (80th percentile) = 10.96 mg l⁻¹ h

Rat NOEL = 8 mg l⁻¹ h

30% inhibition pSMAD

BED

% pSMAD inhibition (AUE/24)

AUC(0,24h) (mg l⁻¹ h)

Total daily dose (mg)

Simulations studies – choosing a PK model (3)

Modifications: only PK

\[
c(t) = \frac{d_k}{V} \frac{k_a}{k_a - CL/V} \left( e^{-(CL/V) t} - e^{-k_a t} \right)
\]

**Parameter** | **Mean value** | **IIV**
--- | --- | ---
\(k_a\) | 2 | 0
\(CL\) | 10 \(\omega_{CL}\) | 
\(V\) | 100 \(\omega_V\) | 

with \(\omega_{CL} = \omega_V \in \{0.3, 0.7\}\)

Simulations studies – link between PK and toxicity

We assumed that the i-th patient shows toxicity if \( s(AUC_i) = \alpha_i AUC_i \geq \tau_T \).

With \( \log \alpha_i \sim N(0, \omega_{\alpha}) \) we obtain

\[
p_T(d_k) = \Phi \left( \frac{\log d_k - \log \tau_T - \log CL}{\sqrt{\omega_C^2 + \omega_{\alpha}^2}} \right)
\]

Varying \( \omega_{\alpha} \)

Varying \( \tau_T \)
### Scenarios and simulated trials settings

<table>
<thead>
<tr>
<th>Scenario</th>
<th>$\tau_T$</th>
<th>$\omega_\alpha$</th>
<th>IIV (CL,V)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1</td>
<td>10.96</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Scenario 2</td>
<td>15.08</td>
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<td>0.7</td>
</tr>
<tr>
<td>Scenario 3</td>
<td>18.1</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Scenario 4</td>
<td>10.96</td>
<td>1.17</td>
<td>0.7</td>
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<tr>
<td>Scenario 5</td>
<td>10.96</td>
<td>0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Scenario 6</td>
<td>10.96</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Scenario 7</td>
<td>10.96</td>
<td>1</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Trials settings:
- 30 patients per trial
- PK, tox at each dose level
- cohorts of 1
- 1000 simulations per scenario
- "no skipping rule"
- methods applied after first toxicity
- 10 sampling points for AUC estimation
find existing approaches (built for specific cases) → modify/adjust them

apply them on the same clinical setting

Comparisons
Scenario 1

τ_T = 10.96
\( \omega_\alpha = 0 \)
IIIV = 0.7

MTD: dose level 4

<table>
<thead>
<tr>
<th>Method</th>
<th>% dose selection</th>
<th>number of DLTs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>PKCOV</td>
<td>0.054</td>
<td>0.015</td>
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<tr>
<td>PKLOG</td>
<td>0.054</td>
<td>0.048</td>
</tr>
<tr>
<td>PKPOP</td>
<td>0.049</td>
<td>0.024</td>
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<td>CRMPK_{L=7.05}</td>
<td>0.104</td>
<td>0.381</td>
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<tr>
<td>CRMPK_{L=10.96}</td>
<td>0.055</td>
<td>0.017</td>
</tr>
<tr>
<td>CRMPK_{L=15.09}</td>
<td>0.030</td>
<td>0.013</td>
</tr>
<tr>
<td>CRMPK_{L=18.1}</td>
<td>0.020</td>
<td>0.014</td>
</tr>
</tbody>
</table>
Scenario 4

\[ \tau_T = 10.96 \]
\[ \omega_\alpha = 1.17 \]
\[ IIIV = 0.7 \]

**MTD:** dose level 2

<table>
<thead>
<tr>
<th>Method</th>
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<th>number of DLTs</th>
</tr>
</thead>
<tbody>
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<td>2</td>
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<tr>
<td>PKCOV</td>
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<td>PKLOG</td>
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<td>PKPOP</td>
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<td>0.291</td>
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<td>0.211</td>
<td>0.536</td>
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<tr>
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<td>0.121</td>
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<tr>
<td>CRMPK_{L=15.09}</td>
<td>0.104</td>
<td>0.433</td>
</tr>
<tr>
<td>CRMPK_{L=18.1}</td>
<td>0.099</td>
<td>0.430</td>
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Scenario 6

\[ \tau_T = 10.96 \]
\[ \omega_\alpha = 0 \]
\[ \text{IlV} = 0.3 \]

MTD: dose level 5

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<tr>
<th>Method</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>number of DLTs</th>
<th>median (n)</th>
<th>min - max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKCOV</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.080</td>
<td>0.672</td>
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<td>PKLOG</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.176</td>
<td>0.704</td>
<td>0.120</td>
<td>5</td>
<td>2</td>
<td>9</td>
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<tr>
<td>PKPOP</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.157</td>
<td>0.667</td>
<td>0.176</td>
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<td>2</td>
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<td>CRMPK(_L=7.05)</td>
<td>0</td>
<td>0.001</td>
<td>0.518</td>
<td>0.481</td>
<td>0</td>
<td>0</td>
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<td>1</td>
<td>4</td>
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<tr>
<td>CRMPK(_L=10.96)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.129</td>
<td>0.820</td>
<td>0.051</td>
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<td>CRMPK(_L=15.09)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.093</td>
<td>0.763</td>
<td>0.144</td>
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<td>CRMPK(_L=18.1)</td>
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<td>0</td>
<td>0</td>
<td>0.093</td>
<td>0.762</td>
<td>0.145</td>
<td>5</td>
<td>2</td>
<td>9</td>
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Scenario 7

\[ \tau_T = 10.96 \]
\[ \omega_a = 1 \]
\[ HIV = 0.3 \]

**MTD:**

**dose level 2**

---

<table>
<thead>
<tr>
<th>Method</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>number of DLTs</th>
<th>median (n)</th>
<th>min - max</th>
</tr>
</thead>
<tbody>
<tr>
<td>PKCOV</td>
<td>0.185</td>
<td>0.114</td>
<td>0.342</td>
<td>0.306</td>
<td>0.050</td>
<td>0.003</td>
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<td>PKLOG</td>
<td>0.114</td>
<td>0.234</td>
<td>0.372</td>
<td>0.232</td>
<td>0.042</td>
<td>0.006</td>
<td>6</td>
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<tr>
<td>PKPOP</td>
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<td>0.182</td>
<td>0.361</td>
<td>0.286</td>
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<td>0.005</td>
<td>6</td>
<td>1</td>
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<td>CRMPK(_L=7.05)</td>
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<td>0.249</td>
<td><strong>0.583</strong></td>
<td>0.153</td>
<td>0</td>
<td>0</td>
<td>6</td>
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<tr>
<td>CRMPK(_L=10.96)</td>
<td>0.009</td>
<td>0.241</td>
<td><strong>0.426</strong></td>
<td>0.286</td>
<td>0.038</td>
<td>0</td>
<td>6</td>
<td>1</td>
<td>11</td>
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<tr>
<td>CRMPK(_L=15.09)</td>
<td>0.008</td>
<td>0.238</td>
<td><strong>0.434</strong></td>
<td>0.280</td>
<td>0.038</td>
<td>0.002</td>
<td>6</td>
<td>1</td>
<td>12</td>
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<td>CRMPK(_L=18.1)</td>
<td>0.007</td>
<td>0.238</td>
<td><strong>0.434</strong></td>
<td>0.282</td>
<td>0.037</td>
<td>0.002</td>
<td>6</td>
<td>2</td>
<td>12</td>
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Distribution of doses – Scenario 1
Distribution of doses – Scenario 4
Distribution of doses – Scenario 6

<table>
<thead>
<tr>
<th></th>
<th>$k_a$</th>
<th>bias</th>
<th>rmse</th>
<th></th>
<th>$V$</th>
<th>bias</th>
<th>rmse</th>
<th></th>
<th>$CL$</th>
<th>bias</th>
<th>rmse</th>
<th></th>
<th>$\omega_V$</th>
<th>bias</th>
<th>rmse</th>
<th></th>
<th>$\omega_{CL}$</th>
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<th>rmse</th>
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<tbody>
<tr>
<td>PKCOV</td>
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<td>0.02975</td>
<td>6.04274</td>
<td>PKCOV</td>
<td>0.02386</td>
<td>0.55869</td>
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<td>0.40827</td>
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<tr>
<td>PKLOG</td>
<td>0.00072</td>
<td>-0.14214</td>
<td>5.97800</td>
<td>PKLOG</td>
<td>0.01751</td>
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<td>PKPOP</td>
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</tbody>
</table>
Conclusions

We compared methods, that include PK measure of exposure (AUC), on different scenarios in case of small population.

We looked at:

**Percentage of MTD selection**

- CRMPK, with the right L, has the best performance
- the best trade-off is CRMPK with larger L

**Estimation of PK parameters**

- despite different distributions of dose allocation, no big difference in estimation
Including only PK measure of exposure, as the AUC, in dose-finding does not increase the percentage of right MTD selection.

**PKCOV**

It depends also on the right $\beta_0$

It is similar to logit($p$) vs log(dose)

...and also PKPOP...

**PKLOG**

- Issue in the estimation when the relationship between tox and AUC is an Heaviside function

**CRMPK**

- Dependence on the threshold $L$

- It tends to CRM alone while $L$ increases
Discussion (2)

- "dose finder"
  - discrete
    - CRM

- "dose estimator"
  - entire curve
    - PK cov
    - PK log
    - PK pop

- CRM PK
Future work

- Moving to Phase I/II including efficacy
  - → binary
  - → continuous

- Including PK/PD estimation during the escalation
  - → full-model based

- Working of priors distributions
  - → combining data from different sources
Aknowledgment

Sarah Zohar
Emmanuelle Comets
Frederike Lents
Corinne Alberti
Nigel Stallard
Tim Friede

Giulia Lestini
France Mentré

Ivelina Gueorguieva

Integrated DEsign and AnaLysis of small population group trials
Bibliography


