Concordance between criteria for covariate model building

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Background

- An aim of PK/PD modelling is to establish parameter-covariate relationships
  - Explain variability between individuals
  - Improve the mechanistic understanding
  - Used for dose individualisation
Parameter variability

Explained by covariates

Between subject variability

Unexplained / random

Explained by covariates

Within subject variability

Unexplained / random

Parameter Variability

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Parameter variability

Note: Assumption that PV = EPV+UPV, PV constant
Criteria for covariate inclusion

- Graphical analysis
  - OFV change
- Statistical significance
  - OFV change
- Clinical relevance
  - drop in UPV
  - Assuming PV=UPV+EPV
  - ?change in EPV/PV

- Subjective & not clear cut
- Commonly used as first/main criteria
- Additional criteria
- Not considered

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Aims

1. Explore correlations between these three criteria ($\Delta EPV$, $\Delta OFV$, $\Delta UPV$) in terms of reliability and signal strength, to judge the significance of a covariate inclusion into a model

2. Is there any benefit in monitoring $\Delta EPV$?

3. What happens to PV?
Methods

• 4 real data set examples (RDSs)
  – No BOV
  – No time-variant covariates
  – Covariates assessed only on one parameter
  – Removed covariates from the full model one at a time and in combination

• Stochastic simulations and estimations (SSEs)
Criteria

• **ΔOFV (NONMEM)**

\[ ΔOFV = OF_{\text{full}} - OF_{\text{reduced}} \]

• **Absolute UPV, EPV, total PV**

\[ \text{UPV} = \left( \sqrt{e^{\omega_P^2}} - 1 \times TVP \right)^2 \]

\( \omega_P^2 \) being the estimated parameter variance and reported by NONMEM in the OMEGA matrix

TVP being the average typical parameter value in the population

\[ \text{EPV} = \text{var}(TVP_i) \quad TVP_i = f(COV_i, \theta_{TVP}, \theta_{COV}) \]

\[ PV = \sqrt{\text{var}(TVP_i) + \left( \sqrt{e^{\omega_P^2}} - 1 \times TVP \right)^2} = EPV + UPV \]

• **Change in EPV, UPV, PV**

\[ \Delta UPV = UPV_{\text{full}} - UPV_{\text{reduced}} \]

\[ \Delta EPV = EPV_{\text{full}} - EPV_{\text{reduced}} \]

\[ \Delta PV = PV_{\text{full}} - PV_{\text{reduced}} \]
Results-RDSs

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Results-RDSs

- PV is changing
- Prazosin: $\Delta \text{UPV} > \Delta \text{EPV}$
- Docetaxel/Moxonidine: $\Delta \text{UPV} < \Delta \text{EPV}$
- Pefloxacin: $\Delta \text{UPV} \approx \Delta \text{EPV}$
- $\Delta \text{OFV}$ correlated with $\Delta \text{UPV}$ and $\Delta \text{EPV}$
  - The higher $\Delta \text{OFV}$, the higher $\Delta \text{UPV}$ & $\Delta \text{EPV}$
SSEs

- 1-compartment intravenous (IV) bolus PK model (Nsim=100)
- 5 samples/subject
- combined RUV

\[ c_{ij} = \frac{Dose}{V_i} \times e^{-\left(\frac{CL_i}{V_i}\right) \times t_j} \]

\[ CL_i = \theta_{TVCL} \times e^{\eta_i,CL} \quad V_i = \theta_{TVV} \times e^{\eta_i,V} \]

- 4 covariates (AA, BB, CC, DD) simulated N(0, 0.09)
  - AA, BB uncorrelated
  - CC, DD correlated 0, 50, 90%
  - All covariates on CL
  - \( \theta_{CL_i} = \theta_{TVCL} \times e^{(\theta_{AA} \times AA_i + \theta_{BB} \times BB_i + \theta_{CC} \times CC_i + \theta_{DD} \times DD_i)} \times e^{\eta_i,CL} \)
SSEs

1. 4 normally distributed covariates AA, BB, CC, DD on CL

2. 2 normally distributed covariates and 2 non-normal distributed covariates
   • CC and DD arising from a t-distribution with heavy tails (DF=4)
     \[ \eta_{t-distributed \, CC/DD} = \eta_i \times \left( 1 + \frac{\eta_i^2+1}{4\theta_{DF}} + \frac{5\eta_i^4+16\eta_i^2+3}{96\theta_{DF}^2} + \frac{3\eta_i^6+19\eta_i^4+17\eta_i^2-15}{38\theta_{DF}^3} \right) \]
   • AA and BB being categorical (bimodal) covariates with values of either -0.21 or +0.21

3. 1 & covariates AA and CC on V

4. 1 & EE (a wrong covariate (N(0, 0.09))) included in the estimations instead of BB or DD

5. 1 & simulated with AA and BB on CL and CC and DD on V, but estimated with all four covariates on CL.
   • 50% correlation between CL and V (as in the standard scenario 1)
   • 0% correlation between CL and V
Results SSEs - PV

- True simulated PV on CL
- Estimated PV on CL with full true model
- Model with removed correlated covariates
- Model with removed uncorrelated covariates
- Reduced covariate models

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Results SSEs - PV

- PV increases with
  - increasing correlation between covariates
  - increasing number of correlated covariates in the model
Results SSEs – $\Delta UPV/\Delta EPV$

- Decreased number of covariates included

- Model with 1 correlated covariate removed
- Model with 1 uncorrelated covariate removed
- Model with removed uncorrelated covariates
- Model with removed correlated covariates

90% correlation between CC and DD

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Results SSEs - ∆UPV

• ∆UPV increases with increasing correlation between covariates in the true full model
• ∆OFV greater if 2 correlated covariates are included compared to 2 uncorrelated covariates
• If only 1 of 2 correlated covariates included in the model ∆UPV small compared to uncorrelated covariates
Results SSEs - $\Delta$EPV

- $\Delta$EPV increases with increasing correlation between covariates in the true model
- If only 1 of 2 highly correlated covariates included in the model EPV can decrease (opposed to increase)
- $\Delta$EPV > $\Delta$UPV
Results SSEs

Correlations between criteria

- Correlation strength between $\Delta EPV$, $\Delta UPV$, $\Delta OFV$
  - $\Delta OFV: \Delta PV < \Delta OFV: \Delta EPV < \Delta OFV: \Delta UPV$
  - $\Delta OFV: \Delta UPV$ stronger if one correlated covariate is excluded

<table>
<thead>
<tr>
<th>Correlation between CC and DD</th>
<th>0%</th>
<th>50%</th>
<th>90%</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\Delta OFV: \Delta PV$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>no AA</td>
<td>-0.34</td>
<td>-0.50</td>
<td>0.66</td>
</tr>
<tr>
<td>no BB</td>
<td>-0.10</td>
<td>-0.26</td>
<td>0.67</td>
</tr>
<tr>
<td>no CC*</td>
<td>-0.15</td>
<td>-0.33</td>
<td>0.67</td>
</tr>
<tr>
<td>no DD*</td>
<td>-0.29</td>
<td>-0.48</td>
<td>0.70</td>
</tr>
<tr>
<td>no AA &amp; BB</td>
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<td>-0.50</td>
<td>0.61</td>
</tr>
<tr>
<td>no CC &amp; DD*</td>
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<td>-0.45</td>
<td>0.66</td>
</tr>
<tr>
<td>no covariates*</td>
<td>-0.32</td>
<td>-0.56</td>
<td>0.62</td>
</tr>
</tbody>
</table>

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Conclusions

• Differentiation between
  – better fit = statistical significance (signal in $\Delta$OFV)
  – clinical significance (signal in $\Delta$EPV/ $\Delta$UPV)
• Generally: better fit results in greater $\Delta$EPV and $\Delta$UPV
• $\Delta$EPV $\neq$ $\Delta$UPV
• PV does not stay the same!
• Monitoring $\Delta$EPV may be beneficial
Questions/Comments

• Thank you for your attention