Model based adaptive optimal designs of adult to children bridging studies using an FDA proposed stopping criteria.

Eric A. Strömberg, PhD candidate
Andrew C. Hooker, Associate Professor of Pharmacometrics

Department of Pharmaceutical Biosciences
Uppsala University
Uppsala, Sweden
In 2012, Wang et al. from the FDA suggested a precision criteria for sample size determination in the design of pediatric PK studies[1].

“The study must be prospectively powered to target a 95% CI [confidence interval] within 60% and 140% of the geometric mean estimates of clearance and volume of distribution for DRUG NAME in each pediatric sub-group with at least 80% power.”

Background

methods for computing the confidence intervals

**NCA**

- For each pediatric sub-group of interest compute geometric mean and SD of derived individual CL and V to compute confidence interval.

**Population PK (NLME)**

- Use estimates from a population PK model to derive typical CL and V predictions in each pediatric sub-group of interest.
Sample size will be dependent on assumptions about method of analysis and the expected variability [2].

Design performance will be dependent on prior information.

Model based adaptive optimal design (MBAOD) has been shown to be less sensitive to initial misspecification in the design stage [3].

Aim

Implement the Wang et al. precision criteria as a stopping criteria in the MBAOD R-Package[4].

In 100 simulated adult to children PK bridging studies:

Compare the design, sample size and power of the MBAOD simulations with standard Optimal Design and NCA sample size estimations according to Wang et al.

https://github.com/andrewhooker/MBAOD
Optimal Design

Design of future study

Model guess $M_0$
Param. Guess $P_0$
Param. Uncertainty $P_{se,0}$
Prior$_0=FIM_0$

Optimal Design

Design

STUDY

Study Population

Data

Estimation

Model ($M$)
Estimates ($P$, $P_{se}$)
Obs. FIM($FIM_{Obs}$)
Optimal Design

**Design of future study**
- Model guess $M_0$
- Param. Guess $P_0$
- Param. Uncertainty $P_{se,0}$
- Prior$_0$ = FIM$_0$

**Optimal Design**

**Simulation**

**Study Population**
- Data

**Estimation**
- Model $(M)$
- Estimates $(P, P_{se})$
- Obs. FIM$(FIM_{obs})$
Optimal Design

Optimal design: PopED [5,6]

http://poped.sourceforge.net

Estimation: NONMEM
Optimal Design

Optimal design: PopED [5,6]

http://poped.sourceforge.net

Estimation: NONMEM
Adaptive Optimal Design

Design of future study 1
Model guesses $M_G^0$
Param. Guess $P_0$
Param. Uncertainty $P_{se,0}$
Prior $P_{0} = \text{FIM}_0$

\[ \text{Optimal Design} \]
Design $(Q_1)$

\[ \text{Simulation} \]
Cohort 1
Data $(Y_1)$
Prior $P_{1}$

\[ \text{Estimation} \]
Possible Models $(M_1)$
Estimates $(P_{1}, P_{se,1})$
Obs. FIM $(\text{FIM}_{obs,1})$

\[ \text{Stopping Criteria Achieved} \]

Design of future study 2

\[ M_1, P_1, P_{se,1} \]
Prior $P_{1}, \text{FIM}_{obs,1}$
New Model guesses $M_G^2$

\[ \text{Optimal Design} \]
Design $(Q_2)$

\[ \text{Simulation} \]
Cohort 2
Data $(Y_2 \pm Y_1)$
Prior $P_{2}$

\[ \text{Estimation} \]
Possible Models $(M_2)$
Estimates $(P_{2}, P_{se,2})$
Obs. FIM $(\text{FIM}_{obs,2})$

\[ \text{Stopping Criteria Achieved} \]

Design of future study $N_c$

\[ M_{Nc-1}, P_{Nc-1}, P_{se, Nc-1} \]
Prior $P_{Nc-1}, \text{FIM}_{obs, Nc-1}$
Model guesses $M_G^{Nc-1}$

\[ \text{Optimal Design} \]
Design $(Q_{Nc})$

\[ \text{Simulation} \]
Cohort $N_c$
Data $(Y_{Nc} \pm Y_{Nc-1} \ldots Y_1)$
Prior $P_{Nc}$

\[ \text{Estimation} \]
Possible Models $(M_{Nc})$
Estimates $(P_{Nc}, P_{se,Nc})$
Obs. FIM $(\text{FIM}_{obs,Nc})$

\[ \text{Stopping Criteria Achieved} \]
Adaptive Optimal Design

Design of future study 1
Model guess $M_{G0}$
Param. Guess $P_0$

Optimal Design
Design ($Q_1$)

Simulation
Cohort 1
Data ($Y_1$)

Estimation
Model ($M_1$)
Estimates ($P_1, P_{se,1}$)
Obs. FIM ($FIM_{Obs,1}$)

Stopping Criteria Achieved

Design of future study 2
$M_1, P_1$
$FIM_{Obs,1}$

Optimal Design
Design ($Q_2$)

Simulation
Cohort 2
Data ($Y_2 \pm Y_1$)

Estimation
Model ($M_1$)
Estimates ($P_2, P_{se,2}$)
Obs. FIM ($FIM_{Obs,2}$)

Stopping Criteria Achieved

Design of future study $Nc$
$M_1, P_{Nc-1}$
$FIM_{Obs, Nc-1}$

Optimal Design
Design ($Q_{Nc}$)

Simulation
Cohort $Nc$
Data ($Y_{Nc} \pm Y_{Nc-1} \ldots Y_1$)

Estimation
Models ($M_1$)
Estimates ($P_{Nc}, P_{se,Nc}$)
Obs. FIM ($FIM_{Obs,Nc}$)

Stopping Criteria Achieved
## The Simulated Study Population

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 - &lt;6 mo</td>
<td>53.05 - &lt;66.1</td>
<td>$a_{1,1}$</td>
<td>$wt_{1,1}$</td>
</tr>
<tr>
<td>2</td>
<td>6 - &lt;12 mo</td>
<td>66.1 - &lt;92.2</td>
<td>$a_{2,1}$</td>
<td>$wt_{2,1}$</td>
</tr>
<tr>
<td>3</td>
<td>1 - &lt;2 y</td>
<td>92.2 - &lt;144.4</td>
<td>$a_{3,1}$</td>
<td>$wt_{3,1}$</td>
</tr>
<tr>
<td>4</td>
<td>2 - &lt;6 y</td>
<td>144.4 - &lt;353.3</td>
<td>$a_{4,1} \ldots a_{4,5}$</td>
<td>$wt_{4,1} \ldots wt_{4,5}$</td>
</tr>
<tr>
<td>5</td>
<td>6 - &lt;12 y</td>
<td>353.3 - &lt;666.5</td>
<td>$a_{5,1} \ldots a_{5,6}$</td>
<td>$wt_{5,1} \ldots wt_{5,6}$</td>
</tr>
<tr>
<td>6</td>
<td>12 - 18 y</td>
<td>666.5 - &lt;1031.9</td>
<td>$a_{6,1} \ldots a_{6,7}$</td>
<td>$wt_{6,1} \ldots wt_{6,7}$</td>
</tr>
<tr>
<td>7</td>
<td>20 - 29 y</td>
<td>1084 - 1553.8</td>
<td>$a_{7,1} \ldots a_{7,10}$</td>
<td>$wt_{7,1} \ldots wt_{7,10}$</td>
</tr>
</tbody>
</table>

PMA: Post Menstrual Age

PK Model and Parameter Scaling

PK Model

\[ y_{ij} = \frac{DOSE_i}{V_i} \left( \frac{CL_i}{V_i} \right)^{\gamma_{ij}} \cdot (1 + \epsilon_{1ij}) + \epsilon_{2ij} \]

Scaling Model

\[ CL_i = CL_{A,i} \left( \frac{WT_i}{70} \right)^{0.75} \left( \frac{PMA_i}{PMA_i + TM50} \right) \]
\[ V_i = V_{A,i} \cdot \left( \frac{WT_i}{70} \right) \]

\[ CL_{A,i}, \ V_{A,i} \in \text{LogNormal} \quad \text{between individuals} \]
\[ \epsilon_{Xij} \in \text{Normal} \quad \text{between observations} \]
\[ DOSE_i = 1000 \cdot \left( \frac{WT_i}{70} \right) \]
### Parameters and Misspecification

#### Parameter Table

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fixed Effects</strong></td>
<td></td>
</tr>
<tr>
<td>(\theta (CL_A))</td>
<td>2.72</td>
</tr>
<tr>
<td>(\theta (V_A))</td>
<td>20.1</td>
</tr>
<tr>
<td>(\theta (TM50))</td>
<td>100 75 150</td>
</tr>
<tr>
<td><strong>Random Effects</strong></td>
<td></td>
</tr>
<tr>
<td>(\omega^2(CL_A))</td>
<td>0.05</td>
</tr>
<tr>
<td>(\omega^2(V_A))</td>
<td>0.05</td>
</tr>
<tr>
<td>(\sigma^2(Prop))</td>
<td>0.015</td>
</tr>
<tr>
<td>(\sigma^2(Add))</td>
<td>0.0001 FIX</td>
</tr>
</tbody>
</table>

#### Scaling of Clearance

![Graph showing scaling of clearance with PMA](image)

**Scaling of Clearance**

- **TM50**
- **100 (T)**

**Mean Clearance**

(Assuming Median WT)

**PMA**

- 0
- 250
- 500
- 750
- 1000
- 1250

**N Children in Total**

- 3 to <6 months
- 6 to <12 months
- 1 to <2 years
- 2 to <6 years
- 6 to <12 years
- 12 to <18 years
- Adults

**TM50**

- 100 (T)
Stopping Criteria

**Cohort Nc**
- Data $(Y_{Nc} \pm Y_{Nc-1} \ldots Y_1)$
- Prior$_{Nc}$

**Estimation**
- Possible Model $(M_{Nc})$
- Estimates $(P_{Nc}, SE_{Nc})$
- Obs. FIM $(FIM_{Obs,Nc})$

**Age Groups 1: 6**
- All Sub Groups

**Median**
- **PMA:**
  - $a_{1,1}$
  - $\ldots$
  - $a_{6,1} \ldots a_{6,7}$

- **WT:**
  - $wt_{1,1}$
  - $\ldots$
  - $wt_{6,1} \ldots wt_{6,7}$

**Median**
- $CL_{1,1}$
- $\ldots$
- $CL_{6,1} \ldots CL_{6,7}$

- $V_{1,1}$
- $\ldots$
- $V_{6,1} \ldots V_{6,7}$

- $SE(CL_{1,1})$
- $\ldots$
- $SE(CL_{6,7})$

- $SE(V_{1,1})$
- $\ldots$
- $SE(V_{6,7})$

% geom. Mean

$CI(CL)_{1,1}$, $CI(CL)_{6,7}$

$CI(V)_{1,1}$, $CI(V)_{6,7}$

Scaling Model
- Param. Estimates
- COV-Matrix
Stopping Criteria

Cohort \( N_c \)

Data \((Y_{N_c} \pm Y_{N_c-1} \ldots Y_1)\)

Prior \(_{N_c}\)

Estimation

Possible Model \((M_{N_c})\)

Estimates \((P_{N_c}, SE_{N_c})\)

Obs. FIM \((FIM_{obs,N_c})\)

Scaling Model

Param. Estimates

COV-Matrix

Age Groups 1: 6

All Sub Groups

Median

PMA:

\(a_{1,1}\)

\(\ldots\)

\(a_{6,1} \ldots a_{6,7}\)

Median

WT:

\(wt_{1,1}\)

\(\ldots\)

\(wt_{6,1} \ldots wt_{6,7}\)

\(CL_{1,1}\)

\(\ldots CL_{6,7}\)

\(V_{1,1}\)

\(\ldots V_{6,7}\)

\(SE(CL_{1,1})\)

\(\ldots SE(CL_{6,7})\)

\(SE(V_{1,1})\)

\(\ldots SE(V_{6,7})\)
Design Approaches

Population model based

**MBAOD**

Prior Information:
Simulated Data from 100 Adults

Initial Design:
9 children in the optimal age group
Fixed sampling schedule.

Optimized variable:
**Age group** from which to add 2
children to the study (using D-optimal design)

**OD**

NCA estimation based

**Adult SD**

Two estimates of variability:
SD of Adult CLi and Vi for all
ped. age groups

**Scaling of CL, V**

SD of scaled parameters for
each age group
Power to reach the stopping criteria was evaluated for the non-adaptive designs using the popPK approach with simulation and estimation.
Restriction of Age Group Inclusion

Group Selection of Unrestricted MBAOD

- Adults
- 12 to <18 years
- 6 to <12 years
- 2 to <6 years
- 1 to <2 years
- 6 to <12 months
- 3 to <6 months

N Children in Total

TM50
- 100 (T)
- 75
- 150
Restriction of Age Group Inclusion

Initial Design (1st Cohort):
9 children in the oldest age group.

Lowest allowed Age Group:
One age group below the age groups which has passed the stopping criteria.
Restriction of Age Group Inclusion

Group Selection of Restricted MBAOD

- Adults
- 9 to <18 years
- 6 to <12 years
- 2 to <6 years
- 1 to <2 years
- 6 to <12 months
- 3 to <6 months

N Children in Total

Simulation Nr
- 66
- 17
- 3

Age Group
Restriction of Age Group Inclusion
OD Stopping Criteria

Design of future study
Model guess $M_0$
Param. Guess $P_0$
Param. Uncertainty $P_{se,0}$
Prior$_0$=FIM$_0$

Optimal Design

Scaling Model Guess
Param. Guess Predicted SE, FIM

Median PMA:
\[
\begin{align*}
a_{1,1} \\
&\vdots \\
a_{6,1} \ldots a_{6,7}
\end{align*}
\]

Median WT:
\[
\begin{align*}
wt_{1,1} \\
&\vdots \\
wt_{6,1} \ldots wt_{6,7}
\end{align*}
\]

\[
\begin{align*}
CL_{1,1} \\
&\vdots \\
CL_{6,1} \ldots CL_{6,7}
\end{align*}
\]

\[
\begin{align*}
V_{1,1} \\
&\vdots \\
V_{6,1} \ldots V_{6,7}
\end{align*}
\]

\[
\begin{align*}
SE(CL_{1,1}) \\
&\vdots \\
SE(CL_{6,7})
\end{align*}
\]

\[
\begin{align*}
SE(V_{1,1}) \\
&\vdots \\
SE(V_{6,7})
\end{align*}
\]
Restriction of Age Group Inclusion

Group Selection of Restricted MBAOD and OD

Age Group
- 3 to <6 months
- 6 to <12 months
- 1 to <2 years
- 2 to <6 years
- 12 to <18 years
- Adults

N Children in Total
- 9
- 11
- 13
- 15
- 17
- 19
- 21
- 23
- 25
- 27
- 29

Simulation Nr
- 66
- 17
- 3
- OD
Results

Total Number of Children

No Misspecification (TM50=100)  Small Misspecification (TM50=75)  Large Misspecification (TM50=150)

Design Approach

MBAOD  OD  Scaling  Adult Prior  MBAOD  OD  Scaling  Adult Prior  MBAOD  OD  Scaling  Adult Prior

N Children in total

(TM50=100)  (TM50=75)  (TM50=150)
Results

Total Number of Children and Power

No Misspecification (TM50=100)

<table>
<thead>
<tr>
<th>Design Approach</th>
<th>N Children in total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBAOD</td>
<td>100</td>
</tr>
<tr>
<td>OD</td>
<td>100</td>
</tr>
<tr>
<td>Scaling</td>
<td>100</td>
</tr>
<tr>
<td>Adult Prior</td>
<td>100</td>
</tr>
</tbody>
</table>

Small Misspecification (TM50=75)

<table>
<thead>
<tr>
<th>Design Approach</th>
<th>N Children in total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBAOD</td>
<td>100</td>
</tr>
<tr>
<td>OD</td>
<td>100</td>
</tr>
<tr>
<td>Scaling</td>
<td>72</td>
</tr>
<tr>
<td>Adult Prior</td>
<td>72</td>
</tr>
</tbody>
</table>

Large Misspecification (TM50=150)

<table>
<thead>
<tr>
<th>Design Approach</th>
<th>N Children in total</th>
</tr>
</thead>
<tbody>
<tr>
<td>MBAOD</td>
<td>100</td>
</tr>
<tr>
<td>OD</td>
<td>100</td>
</tr>
<tr>
<td>Scaling</td>
<td>70</td>
</tr>
<tr>
<td>Adult Prior</td>
<td>70</td>
</tr>
</tbody>
</table>
Conclusions

The FDA precision criteria was implemented as a stopping criteria in the MBAOD R-Package:

- The MBAOD required less children to fulfill the precision criteria than the traditional sample size estimation methodologies
- Power for non-adaptive OD was lower than the required >80%

Any PK or scaling model could be used with this stopping criteria
Acknowledgements

This work was supported by the DDMoRe project. (www.ddmore.eu)

Github repository: https://github.com/IgnisDivne/mbaod_sim