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

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Background

Precision Criteria for pediatric PK studies

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**."

[1] **Yaning Wang** *et al.* "Clarification on precision criteria to derive sample size when designing pediatric pharmacokinetic studies."
J Clin Pharmacol 2012;52:1601-1606

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.

Background

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].

[2] Salem *et al.,* JCP, 2013, [3] Maloney *et al.,* JCP, 2007

Aim

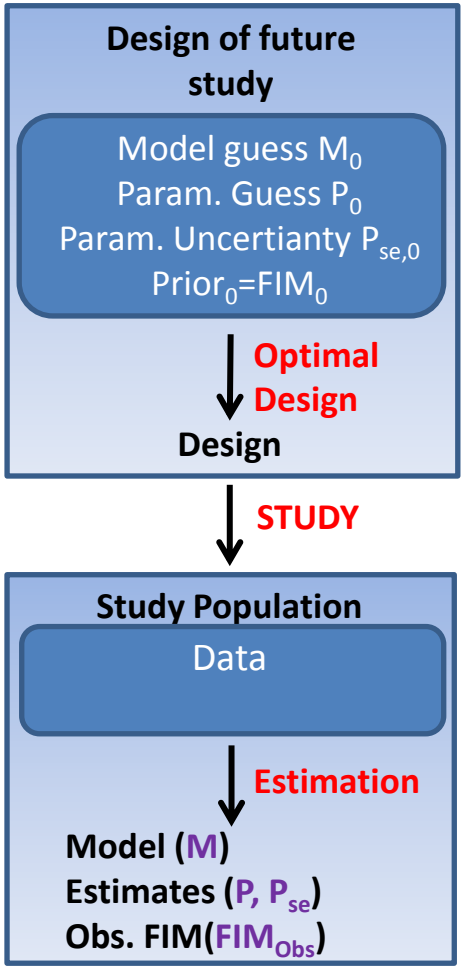
Implement the Wang *et al.* **precision criteria** as a **stopping criteria** in the **MBAOD R-Package[4].**

In 100 simulated adult to children PK bridging studies:

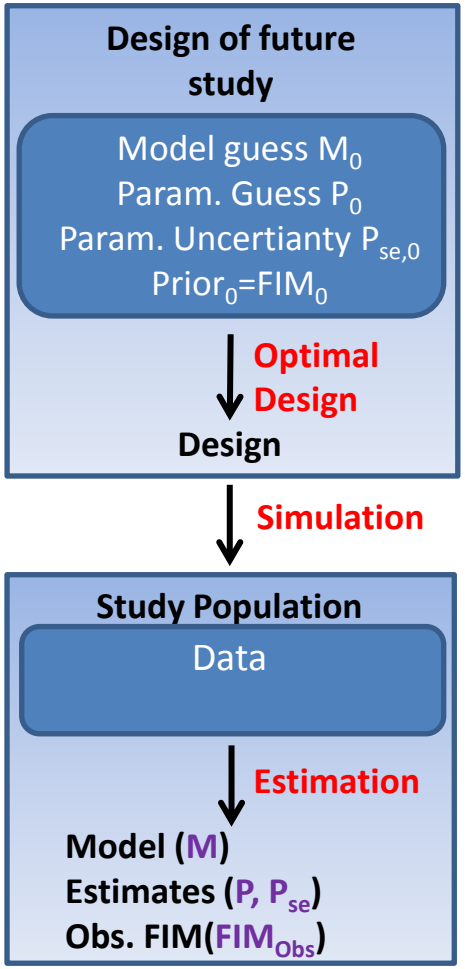
Compare the **design, sample size and power** of the **MBAOD** simulations with standard **Optimal Design** and **NCA sample size estimations** according to **Wang *et al.***

[4] Hooker *et al.* 2013, PAGE 22, Abstract 2952
https://github.com/andrewhooker/MBAOD

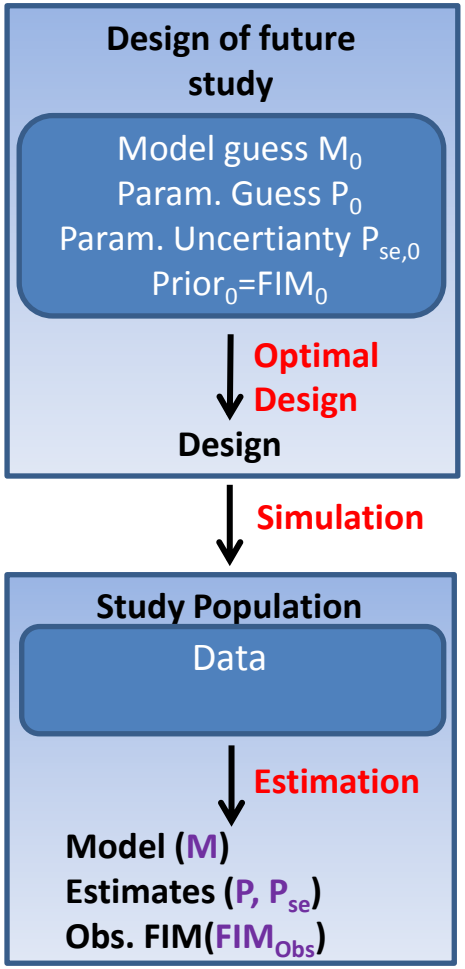
Optimal Design



Optimal Design



Optimal Design

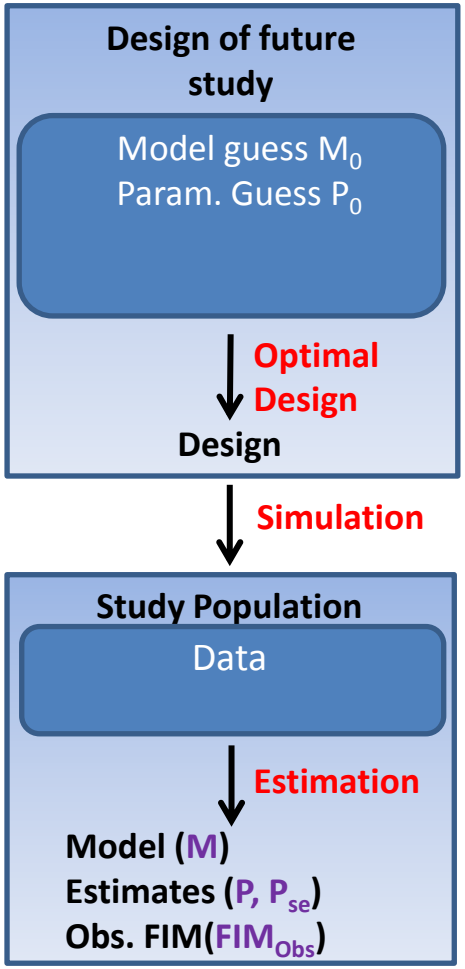


Optimal design: PopED [5,6]

[5] Nyberg et. al. CMPB, 2012.
[6] Foracchia et. al., CMPB, 2004.
http://poped.sourceforge.net

Estimation: NONMEM

Optimal Design



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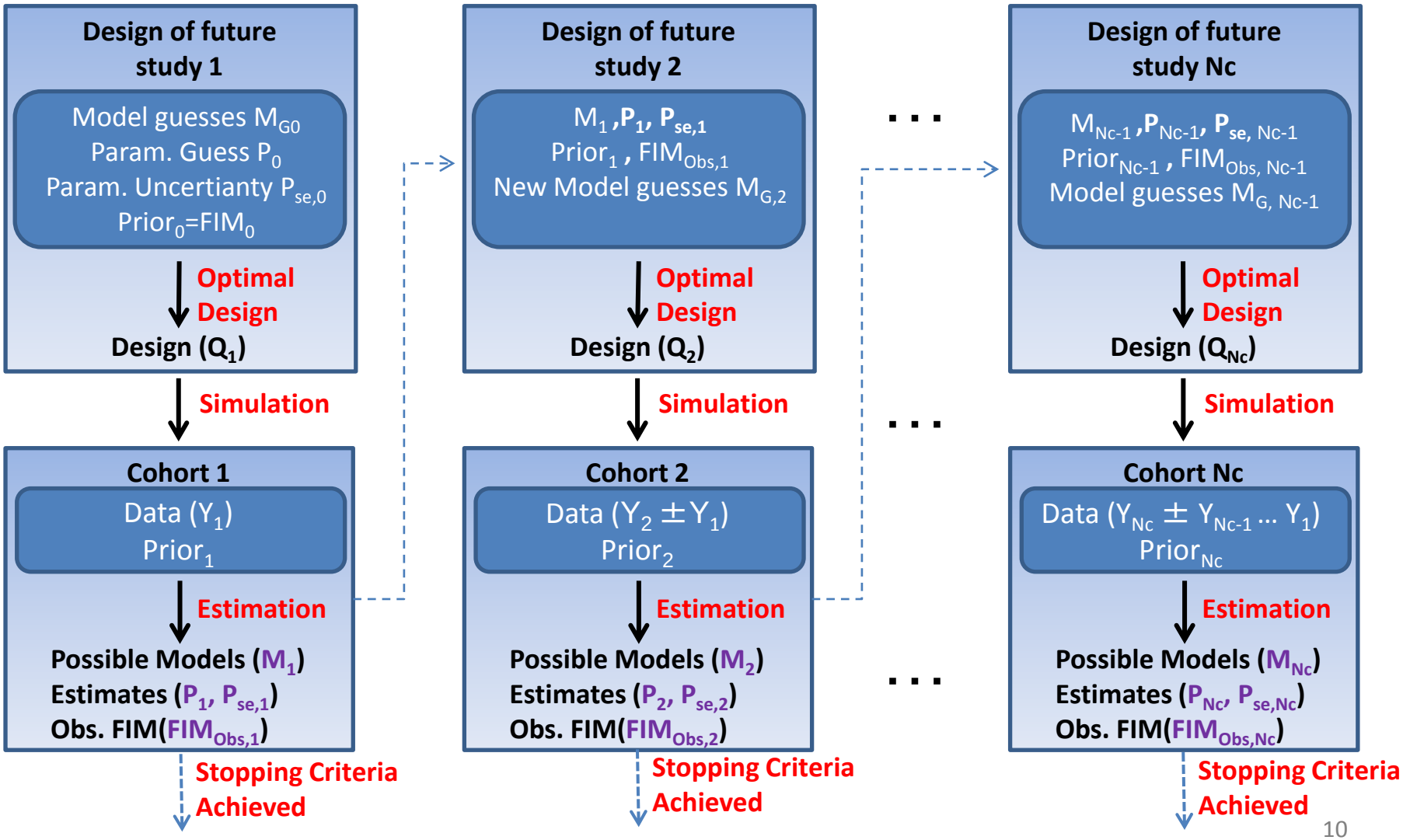
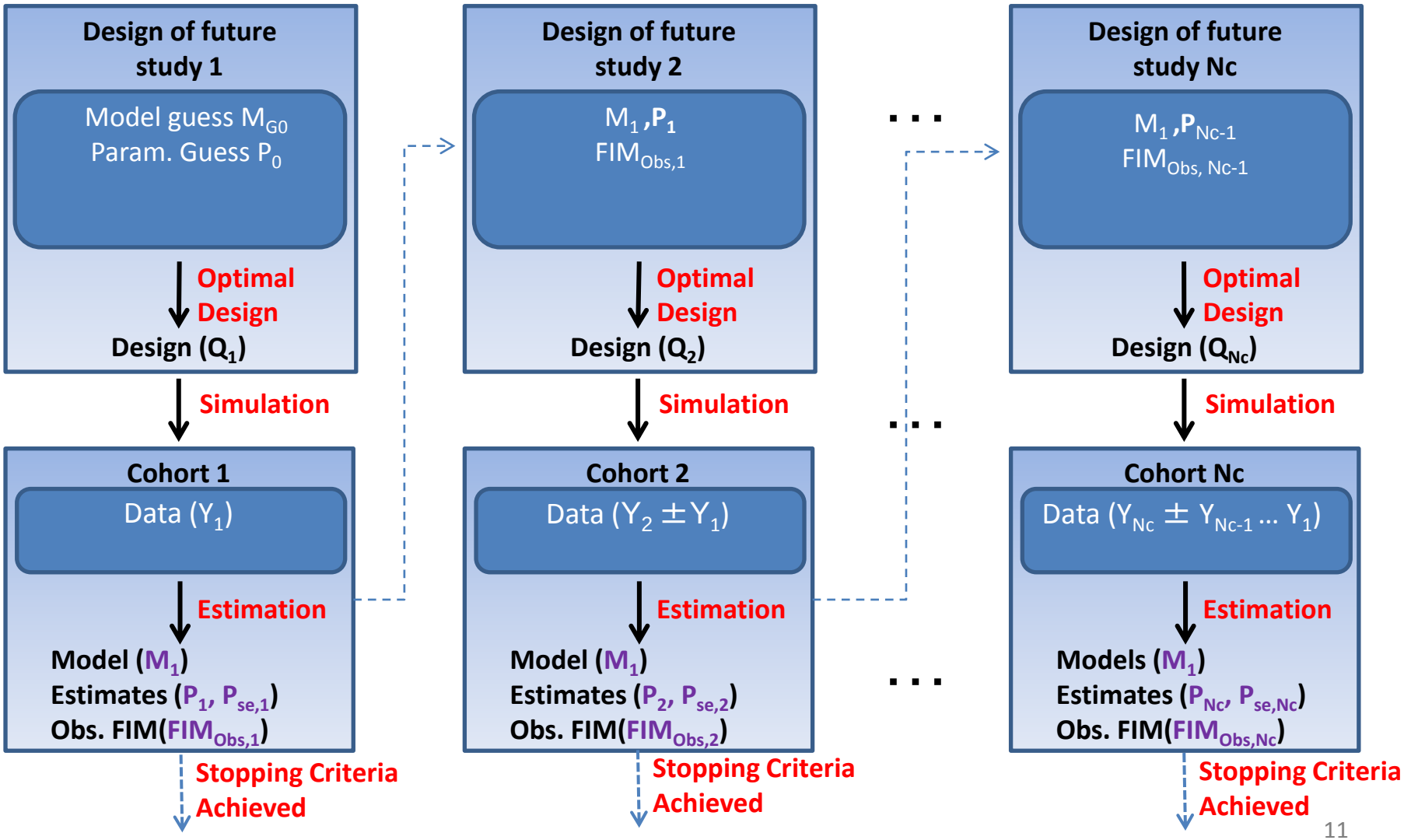
Estimation: NONMEM

Adaptive Optimal Design



Adaptive Optimal Design



The Simulated Study Population

Age Group	Age Range	PMA Range [Weeks]	Sub Groups PMA [5]	Sub Groups WT [5]
1	3 - <6 mo	53.05 - <66.1	$a_{1,1}$	$wt_{1,1}$
2	6 - <12 mo	66.1 - <92.2	$a_{2,1}$	$wt_{2,1}$
3	1 - < 2 y	92.2 - <144.4	$a_{3,1}$	$wt_{3,1}$
4	2 - <6 y	144.4 - <353.3	$a_{4,1} \dots a_{4,5}$	$wt_{4,1} \dots wt_{4,5}$
5	6 - <12 y	353.3 - <666.5	$a_{5,1} \dots a_{5,6}$	$wt_{5,1} \dots wt_{5,6}$
6	12 - 18 y	666.5 - <1031.9	$a_{6,1} \dots a_{6,7}$	$wt_{6,1} \dots wt_{6,7}$
7	20 - 29 y	1084 - 1553.8	$a_{7,1} \dots a_{7,10}$	$wt_{7,1} \dots wt_{7,10}$

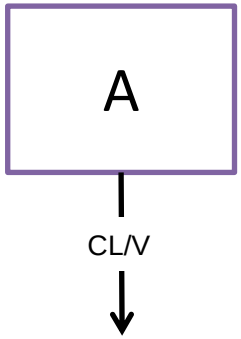
PMA: Post Menstrual Age

[5] Fryar *et al*. "Anthropometric reference data for children and adults: United States, 2007–2010." National Center for Health Statistics. Vital Health Stat 11(252). 2012.

PK Model and Parameter Scaling

PK Model

$$y_{ij} = \frac{DOSE_i}{V_i} e^{-\left(\frac{CL_i}{V_i}\right)\cdot t_{ij}} \cdot (1+\varepsilon_{1ij}) + \varepsilon_{2ij}$$



Scaling Model

$$CL_i = CL_{A,i}\left(WT_i / 70\right)^{0.75}\left(\frac{PMA_i}{PMA_i + TM50}\right)$$

$$V_i = V_{A,i}\cdot\left(WT_i / 70\right)$$

TM50: Maturation Half-life

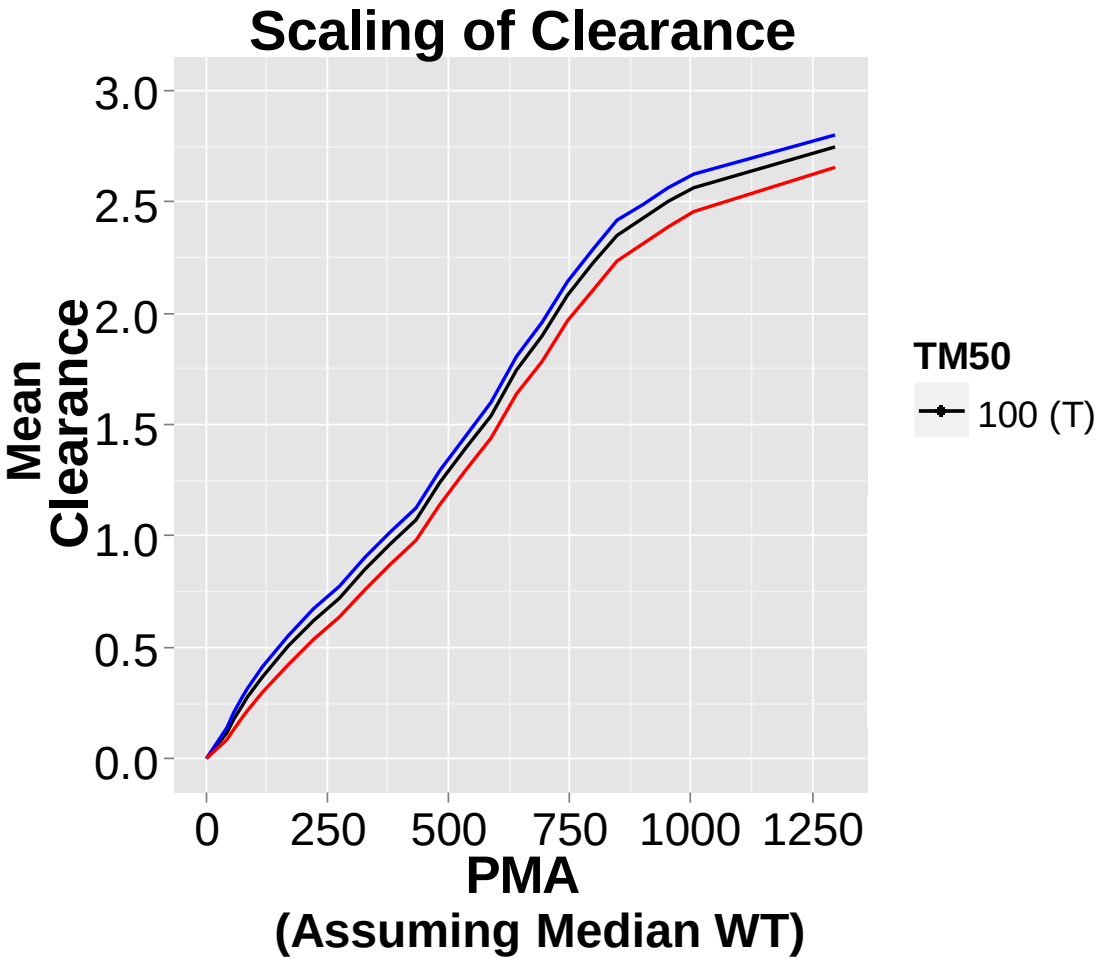
$CL_{A,i},\ V_{A,i} \in LogNormal$ between individuals

$\varepsilon_{Xij} \in Normal$ between observations

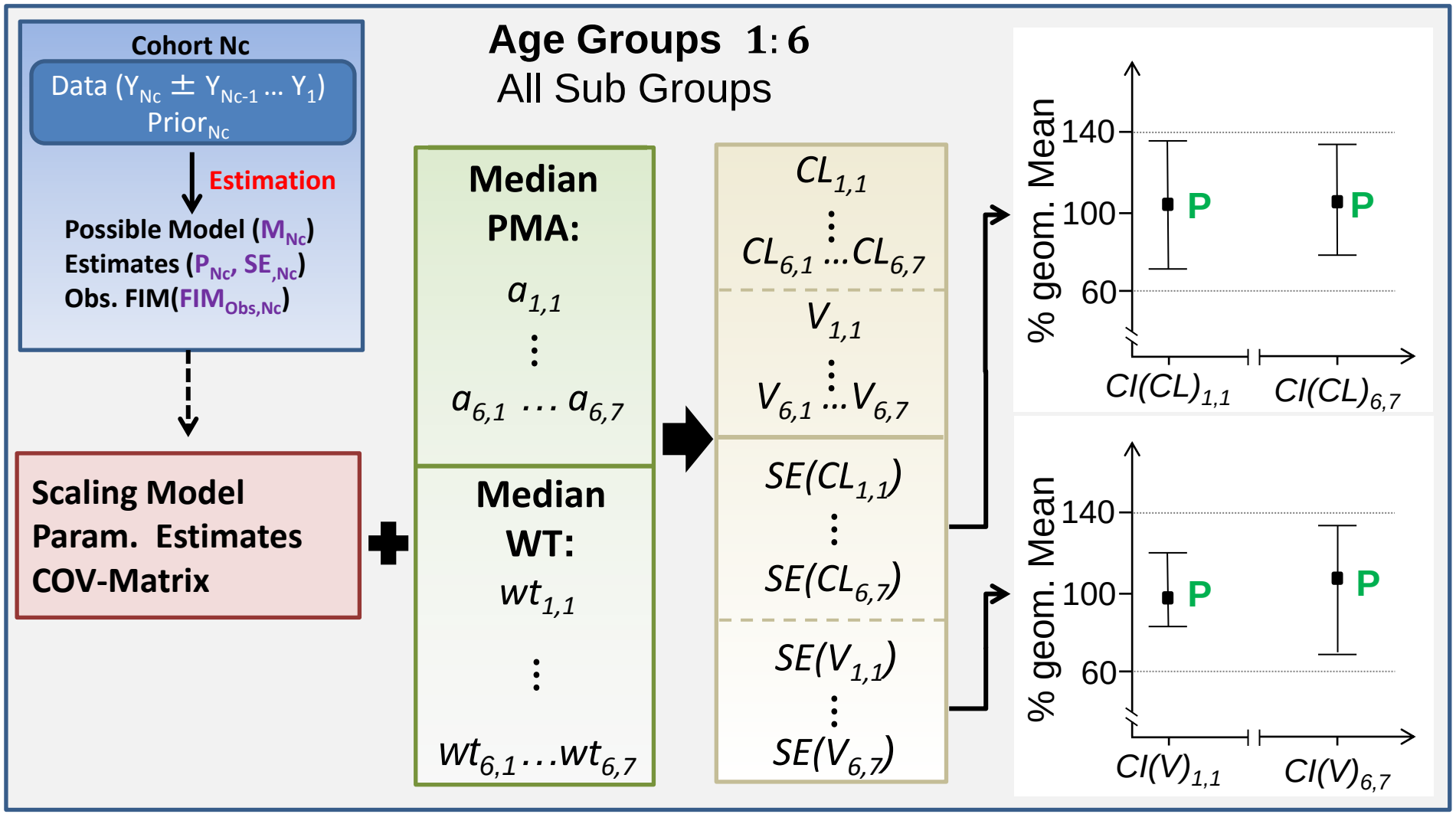
$$DOSE_i = 1000\cdot\left(WT_i / 70\right)$$

Parameters and Misspecification

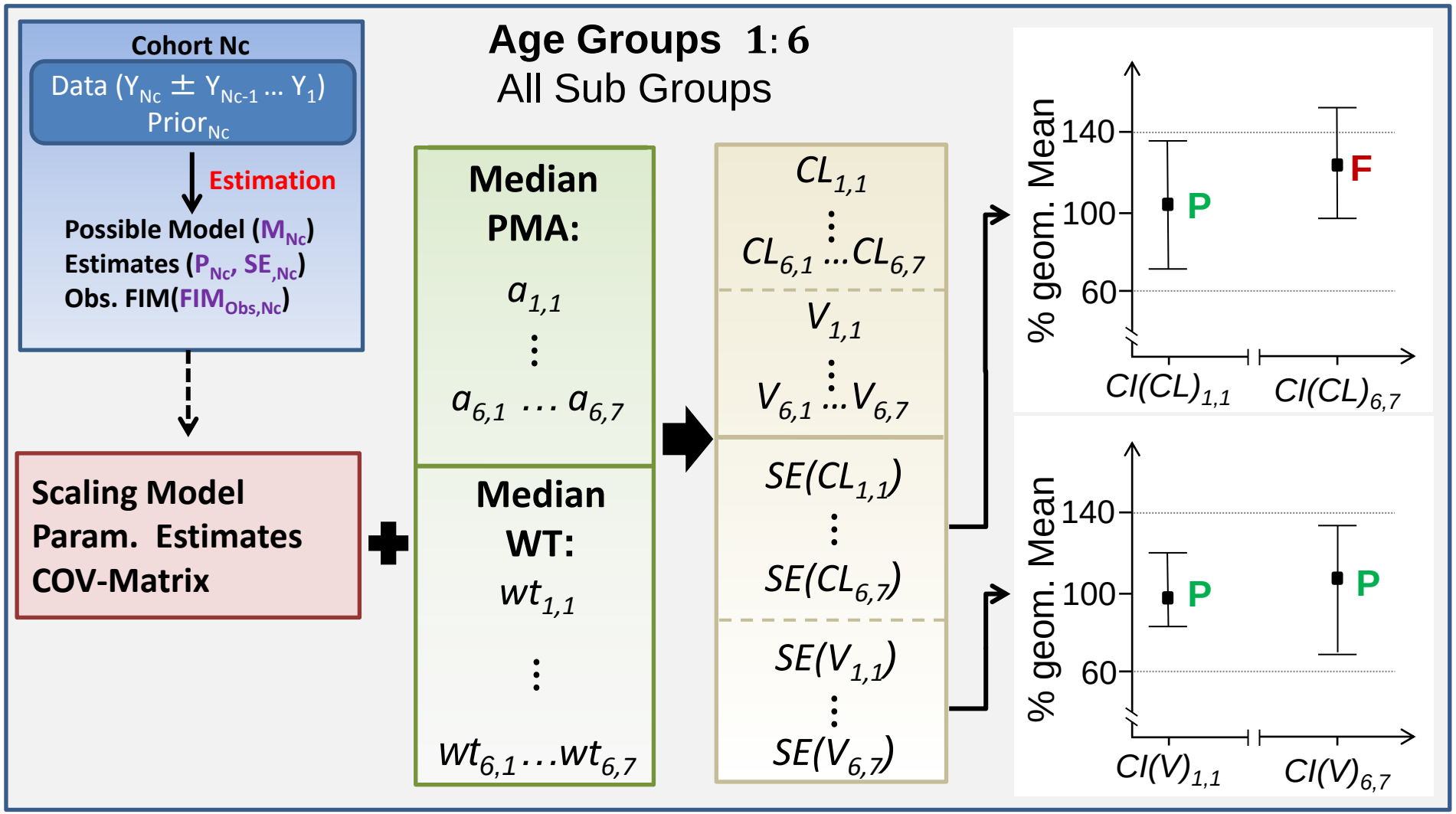
Parameter	Value
Fixed Effects	
θ (CL_A)	2.72
θ (V_A)	20.1
θ (TM50)	100 **75** **150**
Random Effects	
$\omega^2(CL_A)$	0.05
$\omega^2(V_A)$	0.05
σ^2(Prop)	0.015
σ^2(Add)	0.0001 FIX



Stopping Criteria



Stopping Criteria



Design Approaches

Population model based

MBAOD

OD

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)

NCA estimation based

Adult SD

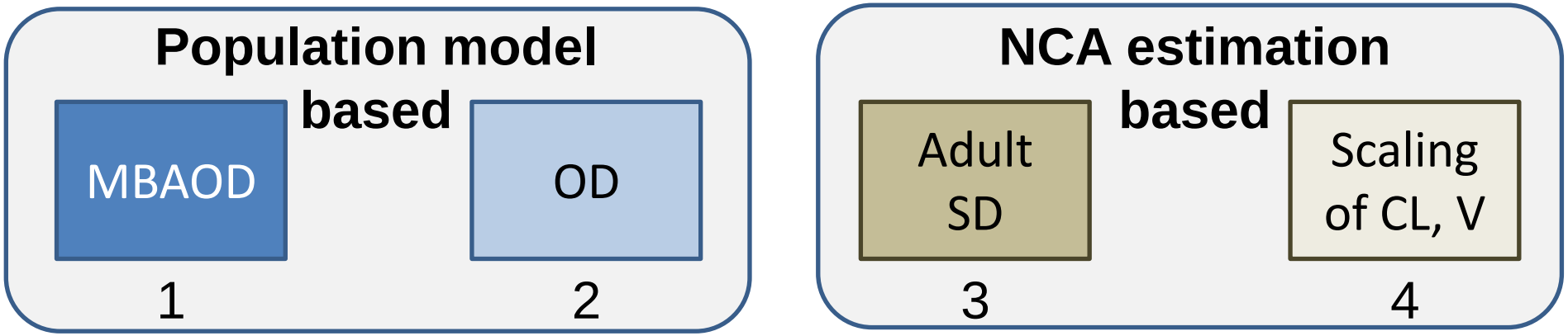
Scaling of CL, V

Two estimates of variability:

SD of Adult CLi and Vi for all ped. age groups

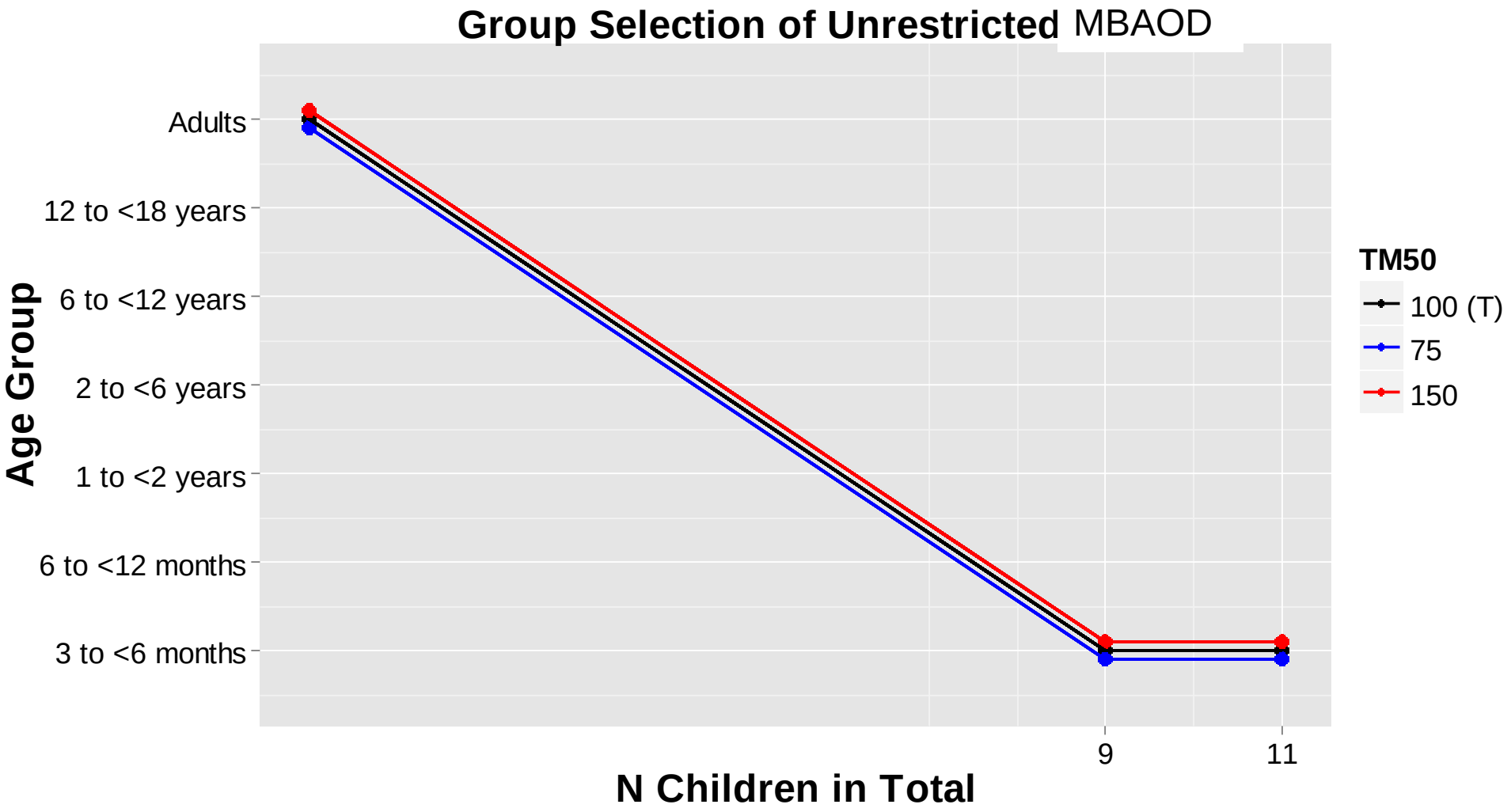
SD of scaled parameters for each age group

Design Approaches



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



Restriction of Age Group Inclusion

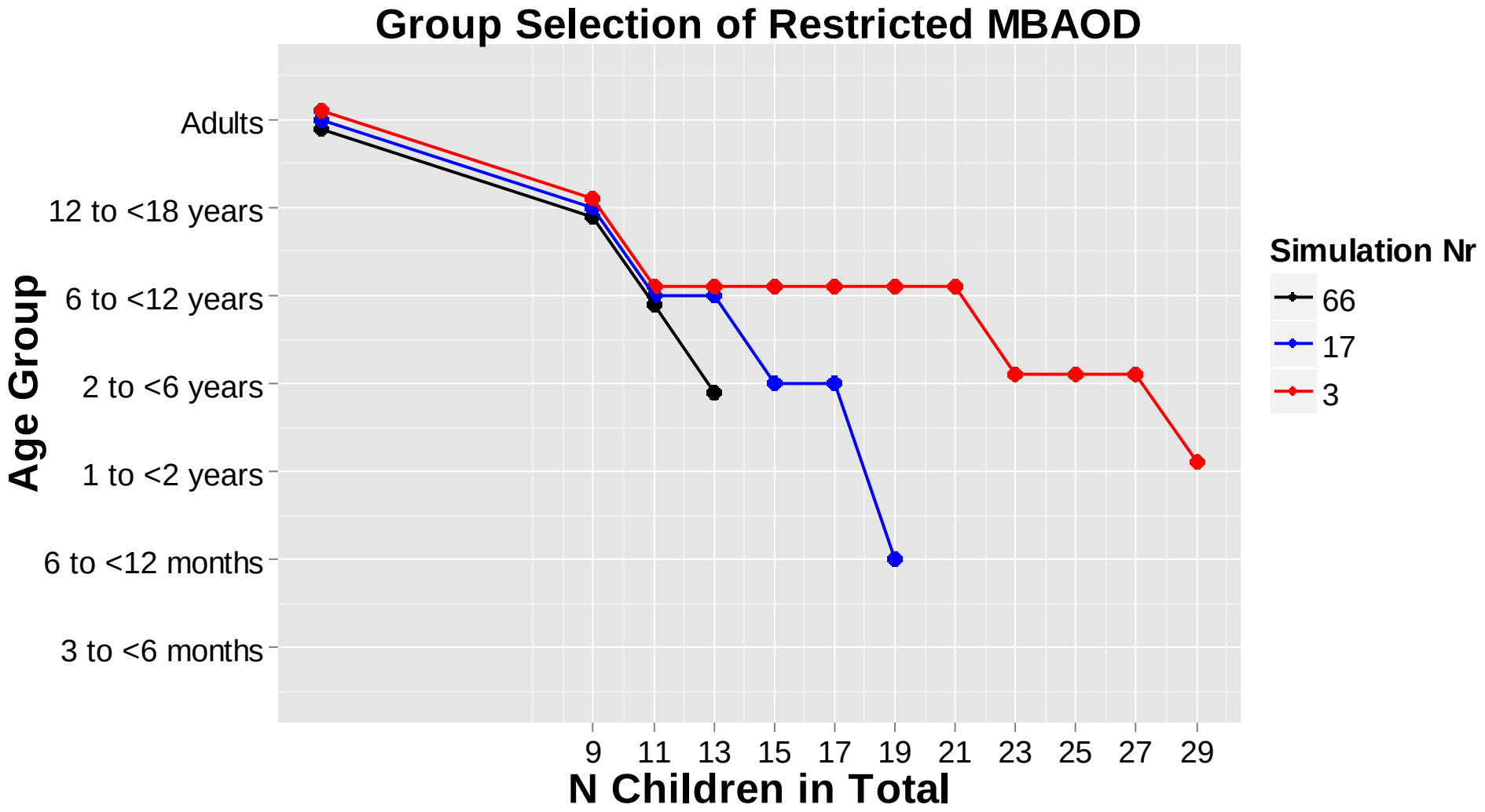
Initial Design (1st Cohort):

9 children in the oldest age group.

Lowest allowed Age Group:

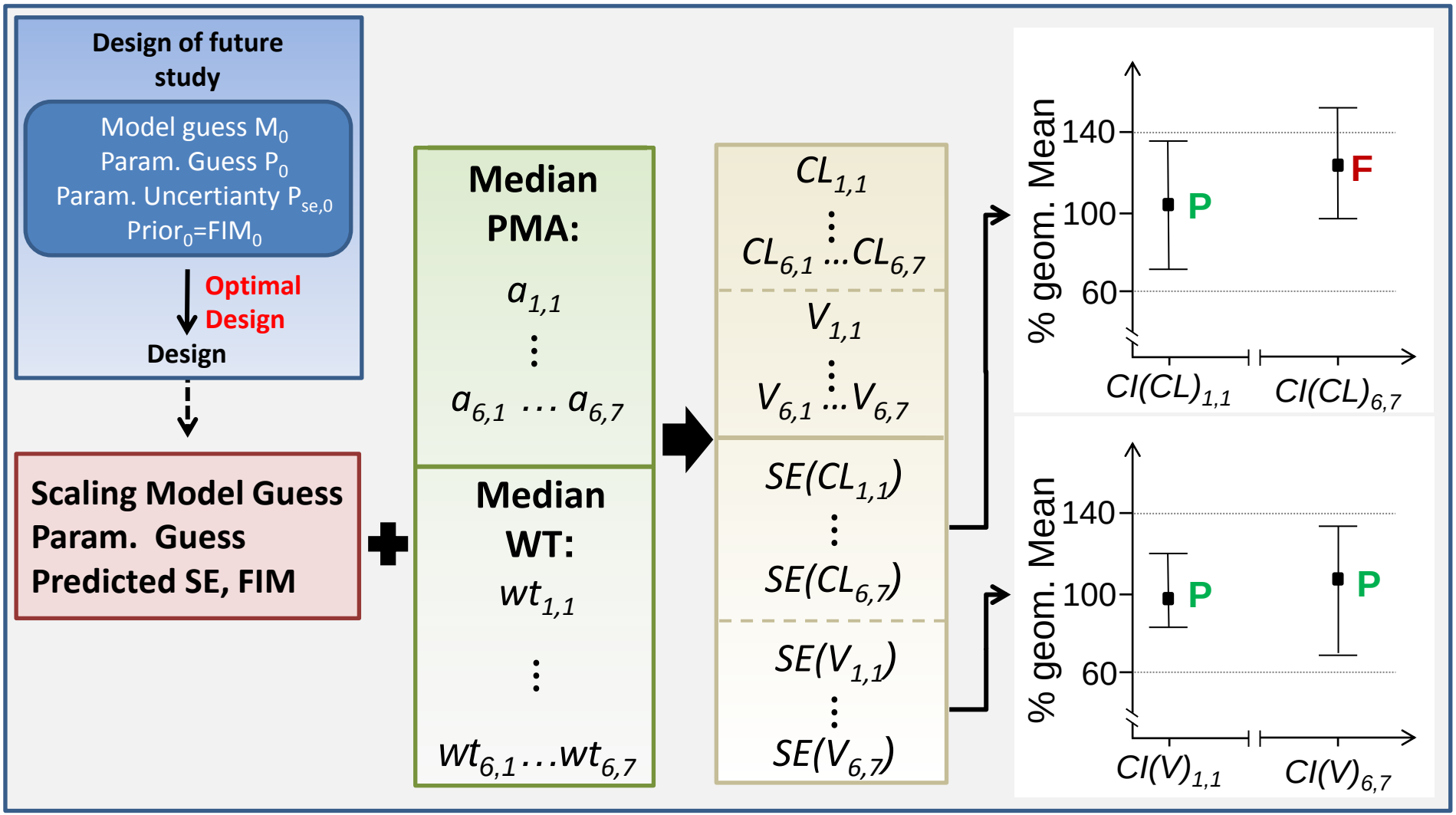
One age group below the age groups which has passed the stopping criteria.

Restriction of Age Group Inclusion



Restriction of Age Group Inclusion

OD Stopping Criteria



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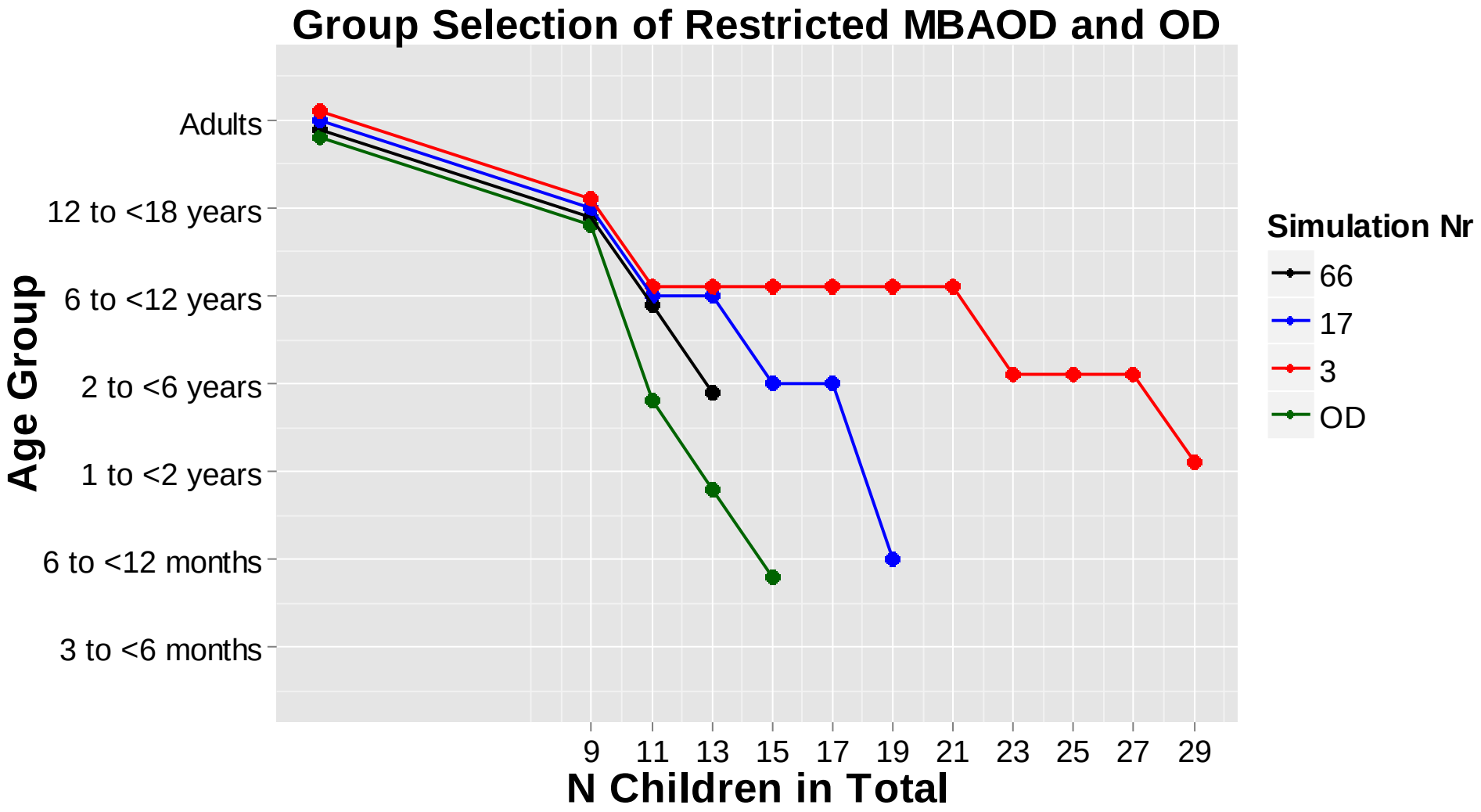
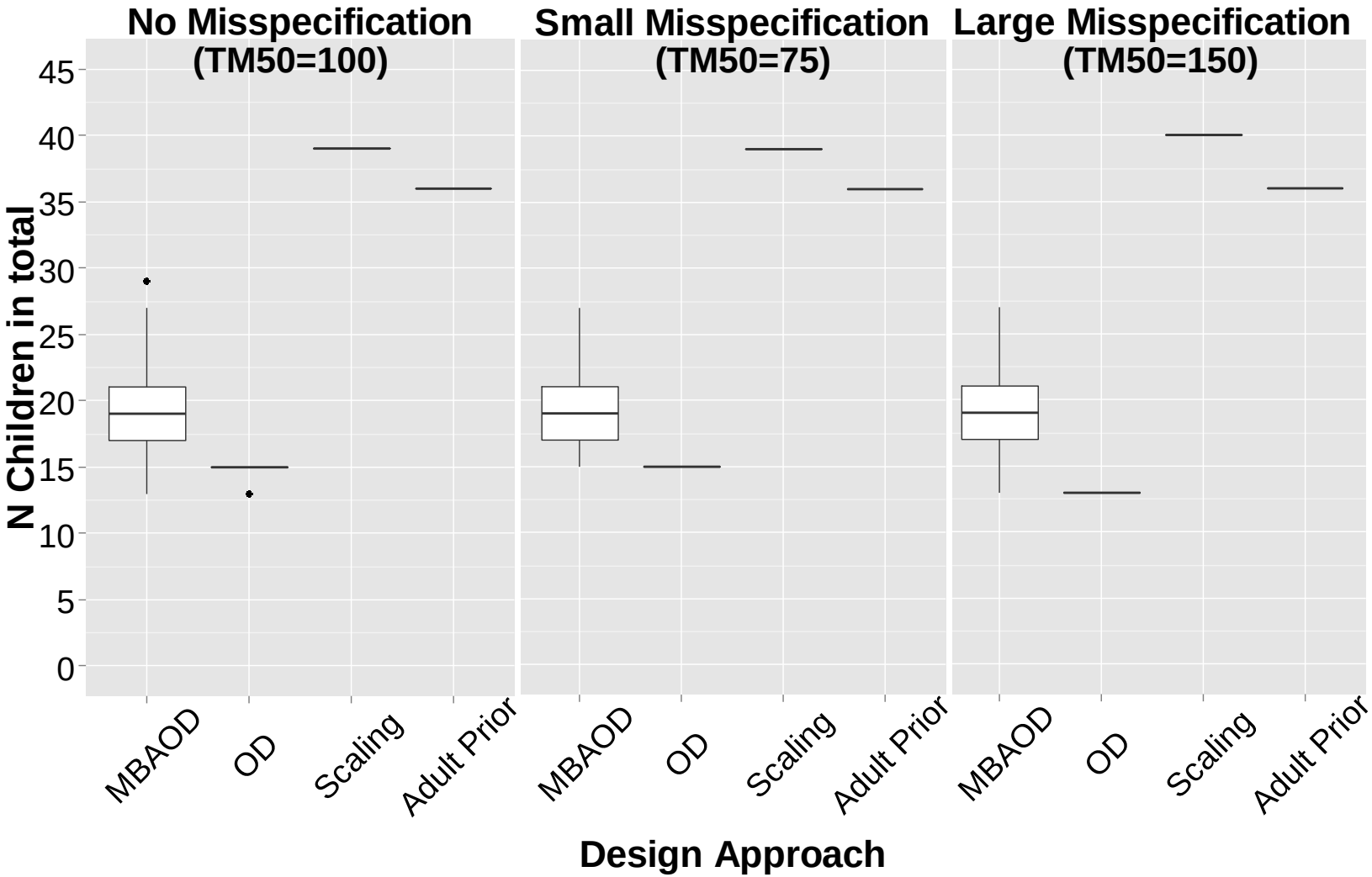


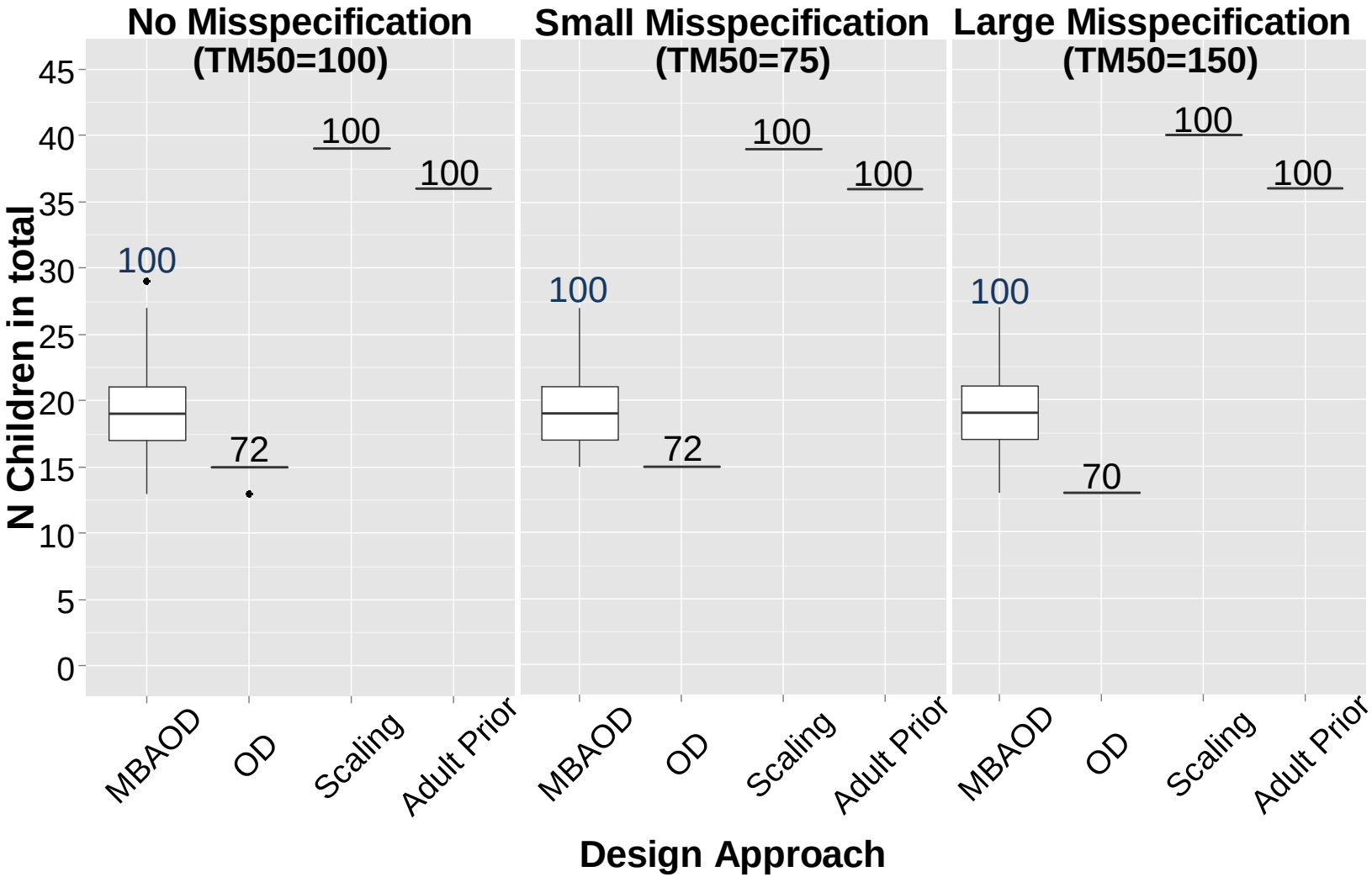
Results

Total Number of Children



Results

Total Number of Children and Power



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

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Acknowledgements

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Drug Disease Model Resources

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