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# Simulated Model Based Adaptive Optimal Design using FDA Stopping Criteria.

## - An Adults to Children Bridging Study Example

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# Background

In traditional design, the size of the study population is regularly determined *a priori* using power calculations.

Wang *et al.* has previously suggested a precision criteria for sample size determinations for design of pediatric PK studies[1].

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# Background

## Precision Criteria

"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

Sample size (and design) will be dependent on source of prior information on 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.* 2014, [3] Maloney *et al.* 2007

# Aim

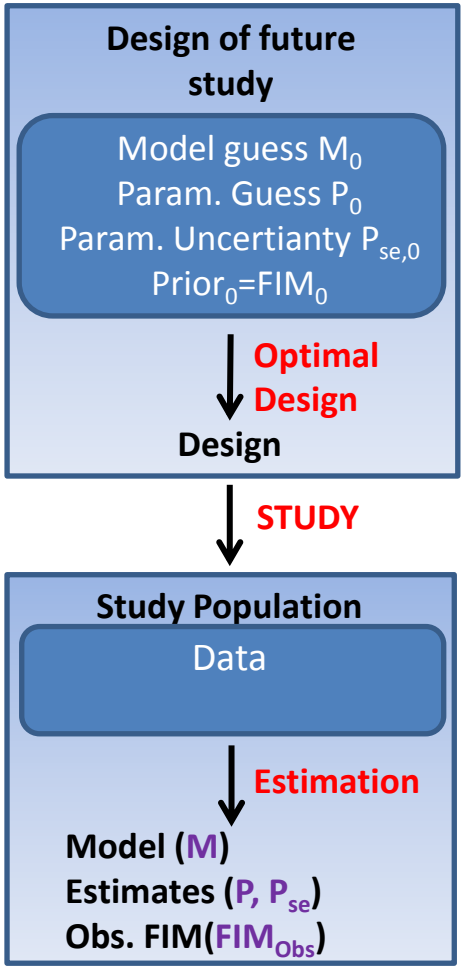
Implement the **precision criteria** as a **stopping criteria** in the **MBAOD R-Package[4].**

In 100 simulated adult to children PK bridging studies:

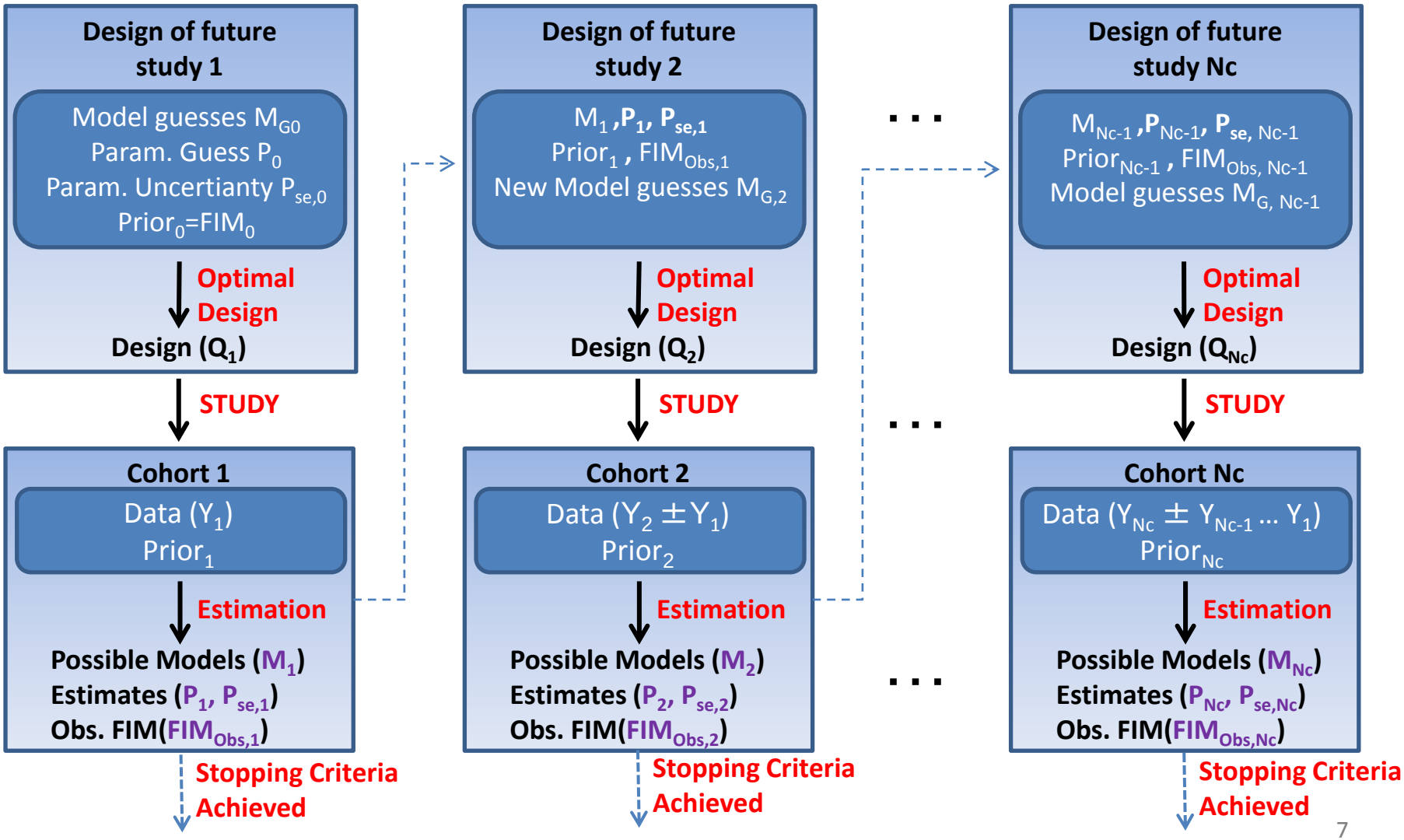
**Compare** the **sample size** of the **MBAOD** simulations with standard **Optimal Design** and **sample size estimation** according to **Wang *et al.***

[4] Hooker *et al.* 2013, PAGE 22, Abstract 2952

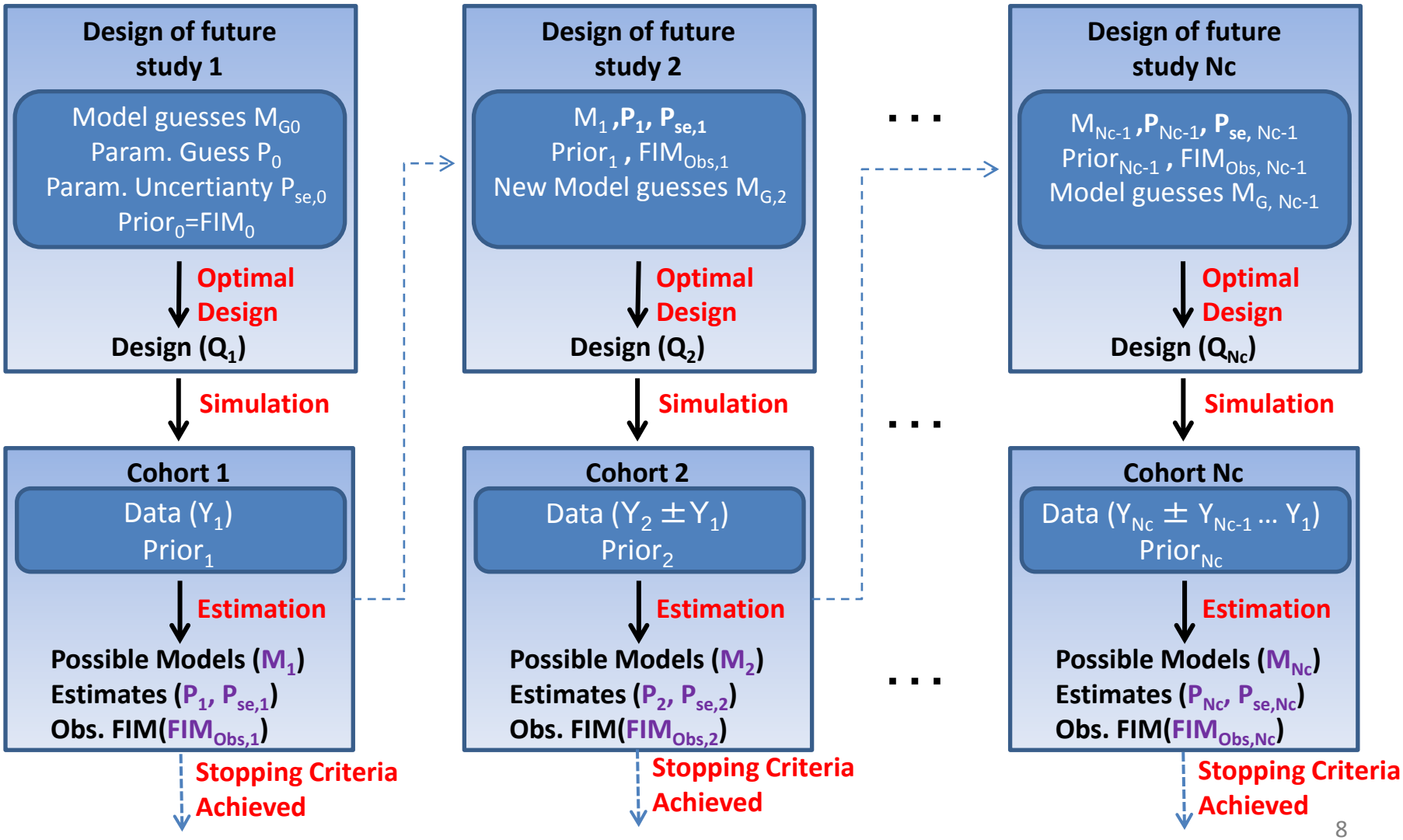
# Optimal Design



# 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**

$$Dose = 1000\frac{WT}{70}$$

$$C = \frac{Dose}{V}e^{\left(-\frac{CL}{V}t\right)}$$

TM50: Maturation Half-life

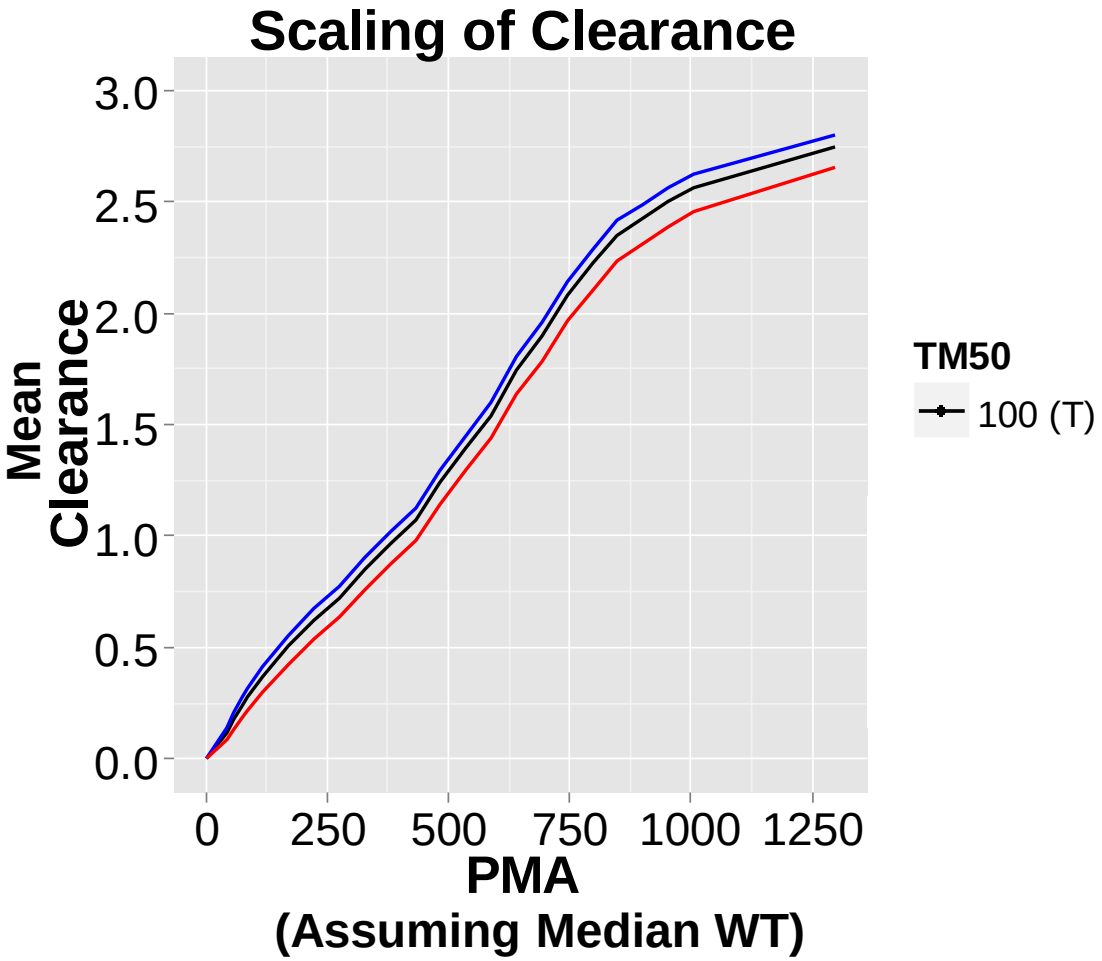
**Parameter Scaling**

$$CL = CL_A\left(\frac{WT}{70}\right)^{0.75}\left(\frac{PMA}{PMA + TM50}\right)$$

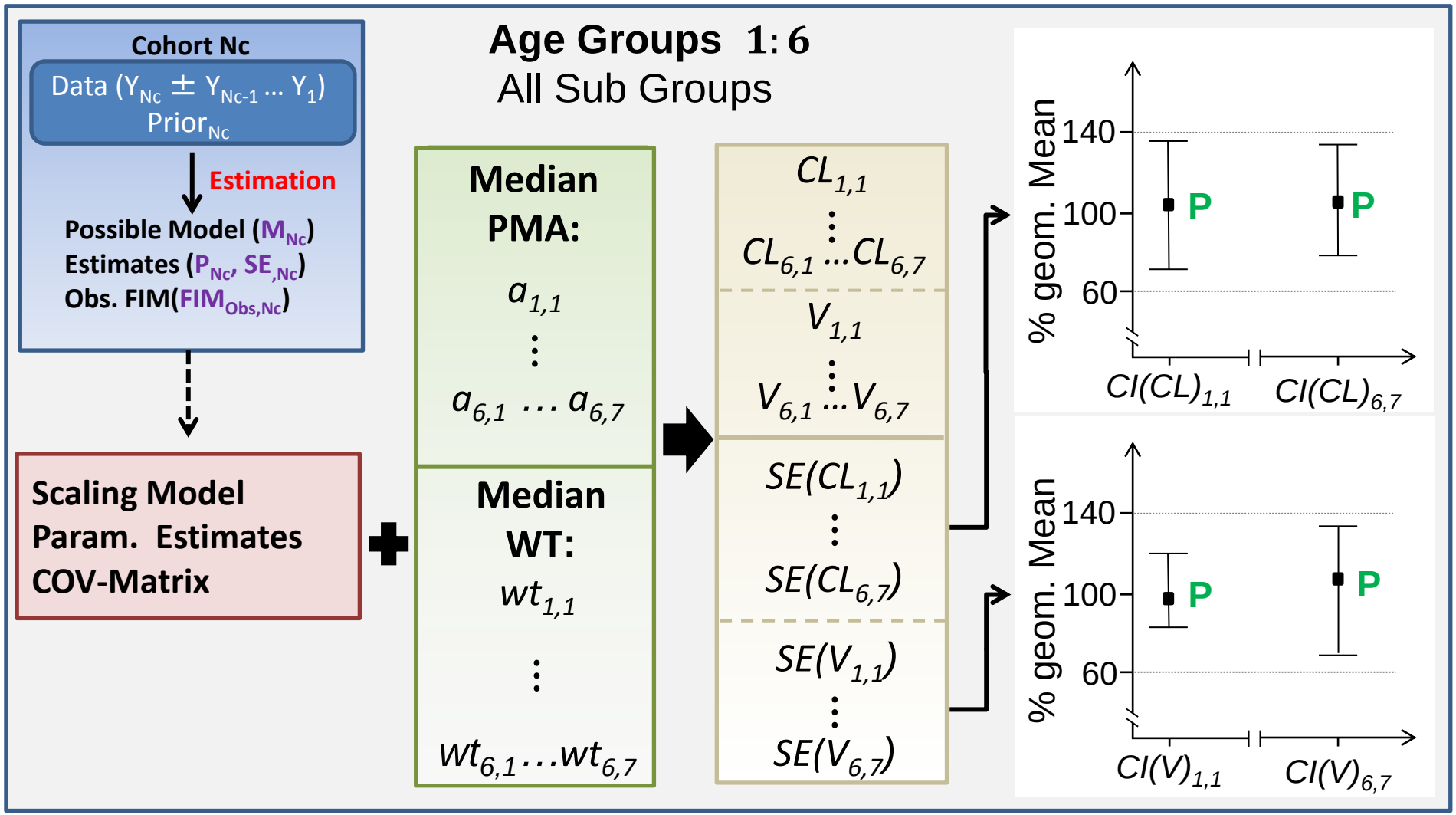
$$V = V_A\left(\frac{WT}{70}\right)^{1}$$

# 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 |
| $\sigma^2$(Prop) | 0.015 |
| $\sigma^2$(Add) | 0.0001 FIX |



# Stopping Criteria



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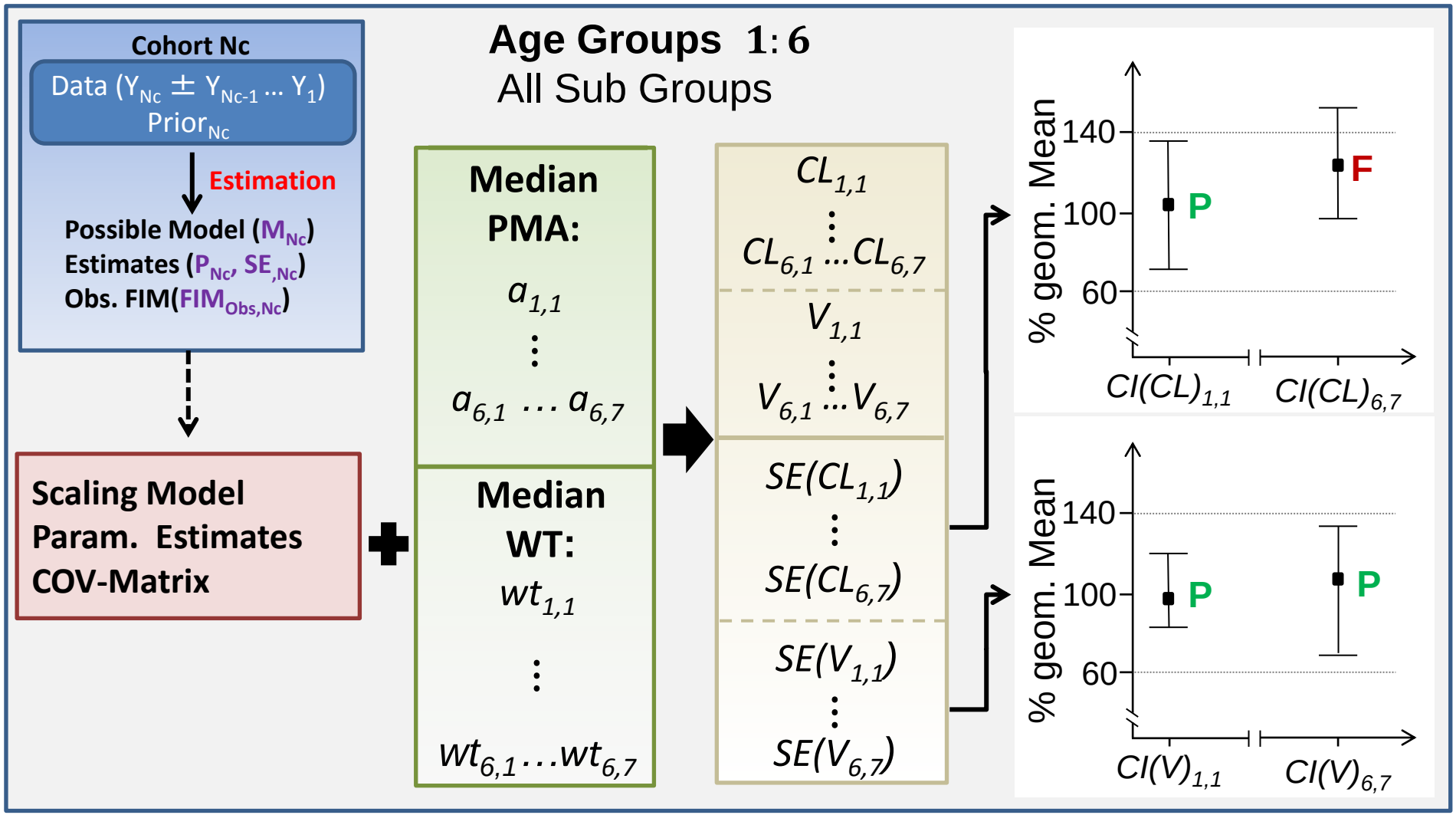


# Design Approaches

## Optimal Design

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

## Sample Size Estimation

Adult SD

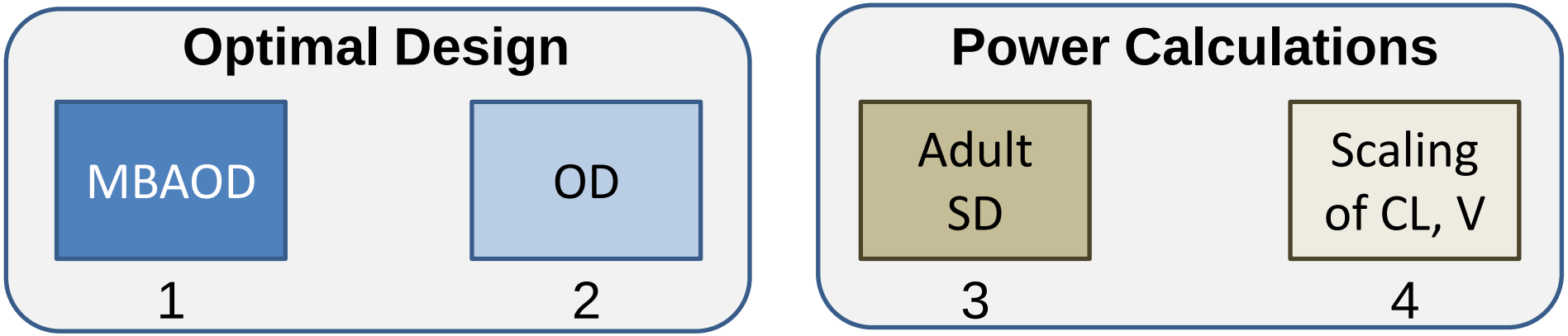
Scaling of CL, V

Two estimates of variability:

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

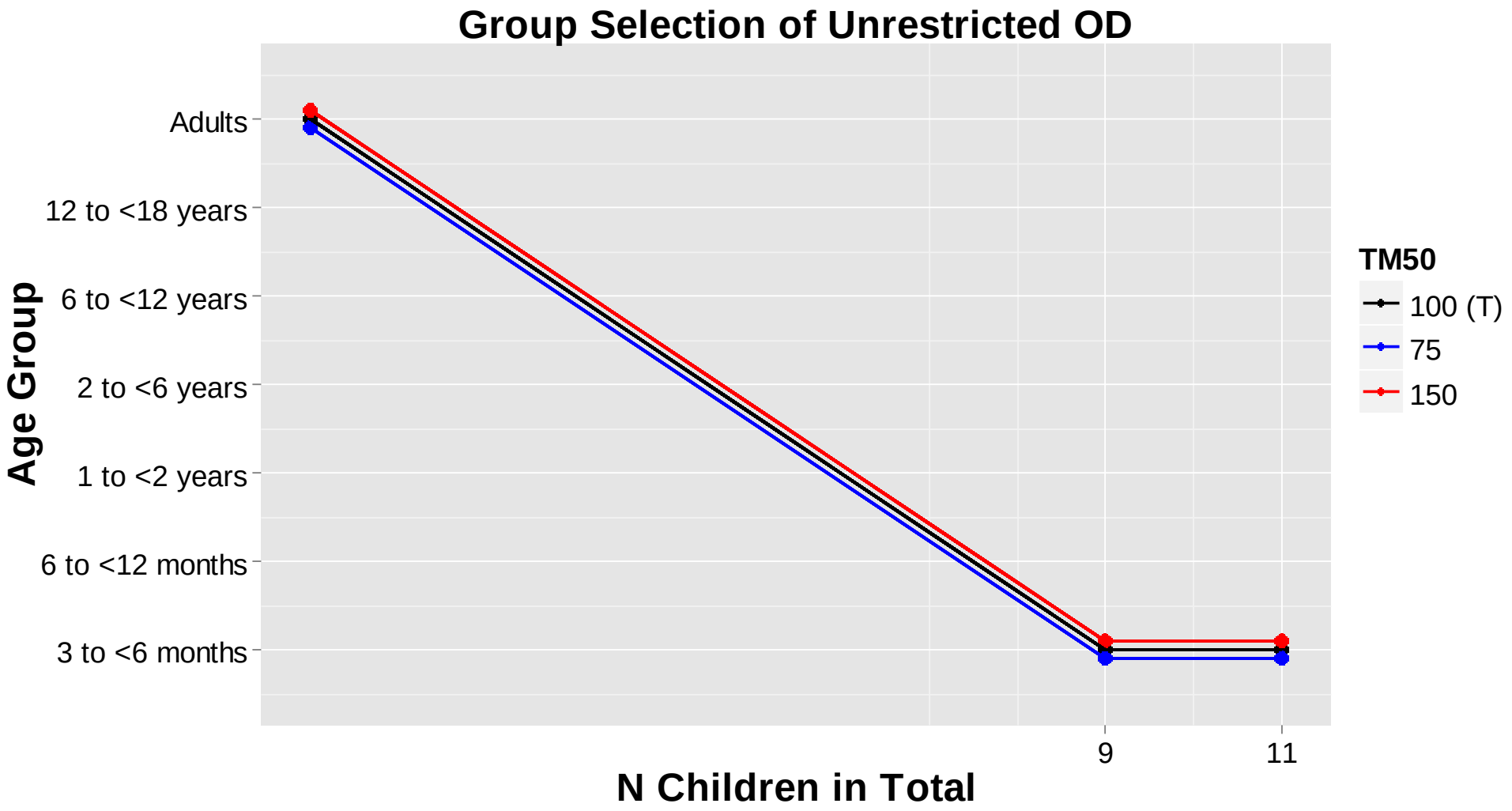
SD of scaled parameters for each age group

# Design Approaches




True power to reach the stopping criteria was evaluated for the non-adaptive designs using simulations and estimations.

# Restriction of Age Group Inclusion



# Restriction of Age Group Inclusion

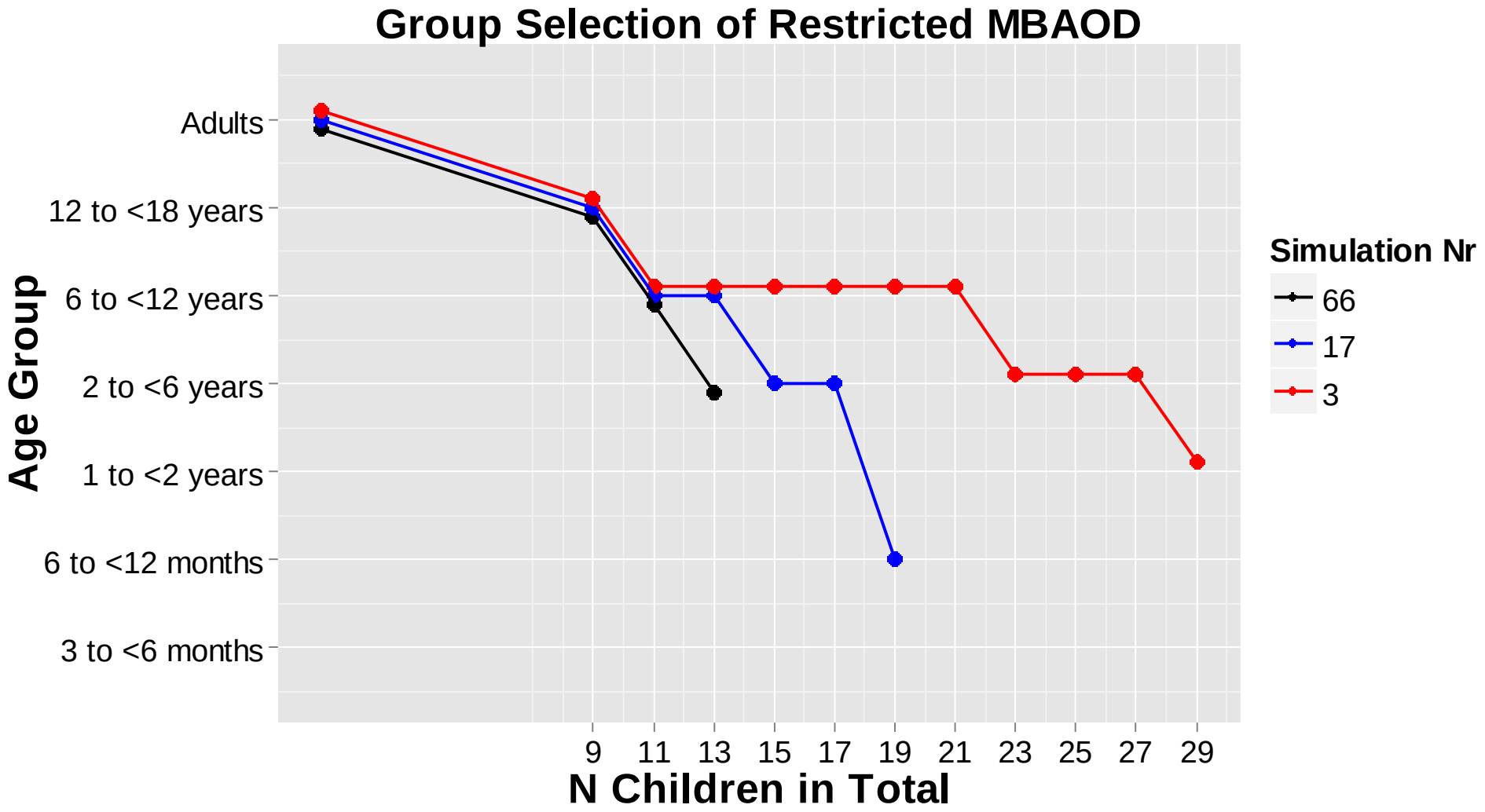
Initial Design (1st Cohort):

9 children in the oldest age group.

Lowest allowed Age Group:

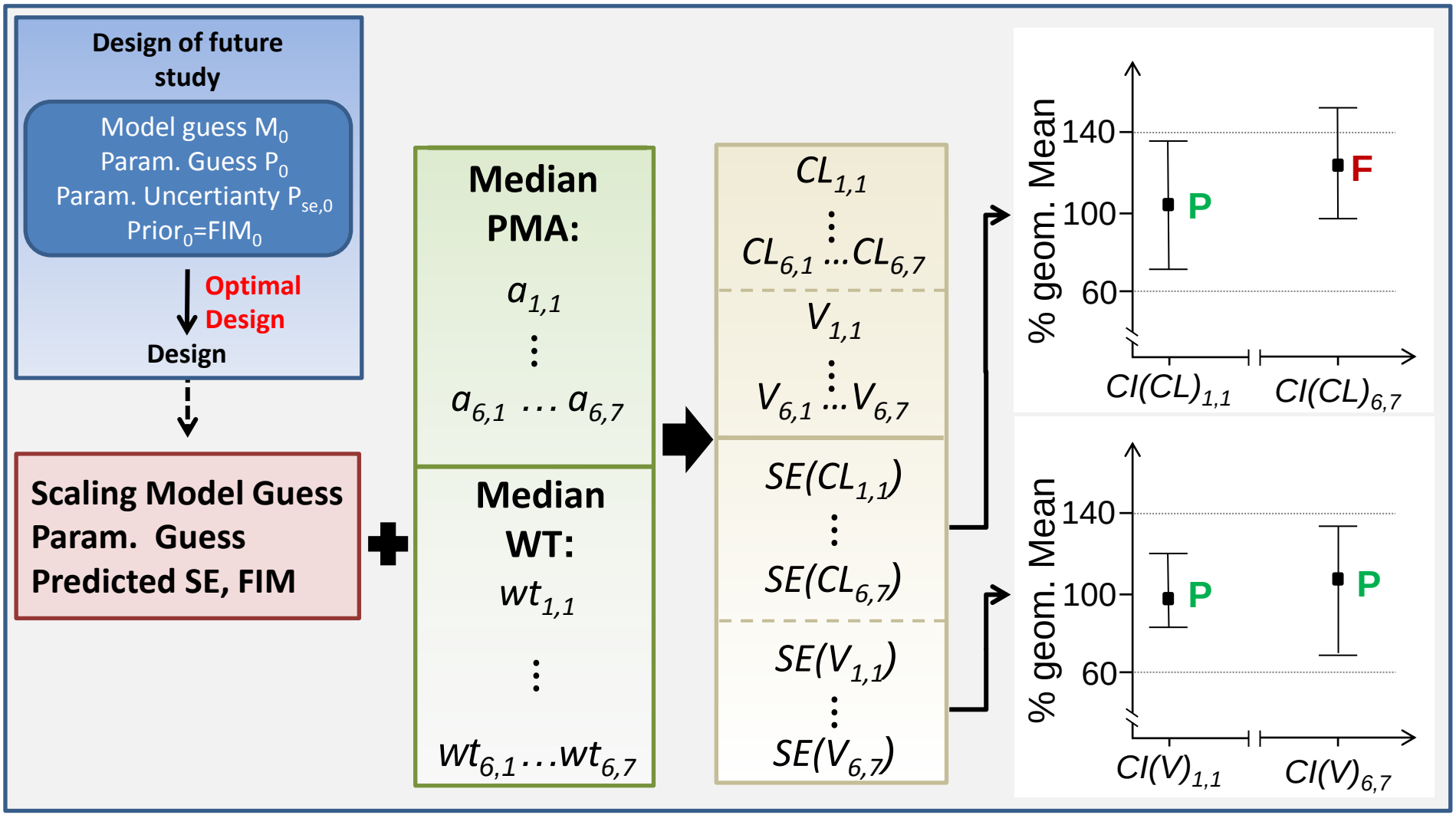
One age group below the age groups which has passed the stopping criteria.

# Restriction of Age Group Inclusion



# Restriction of Age Group Inclusion

## OD Stopping Criteria



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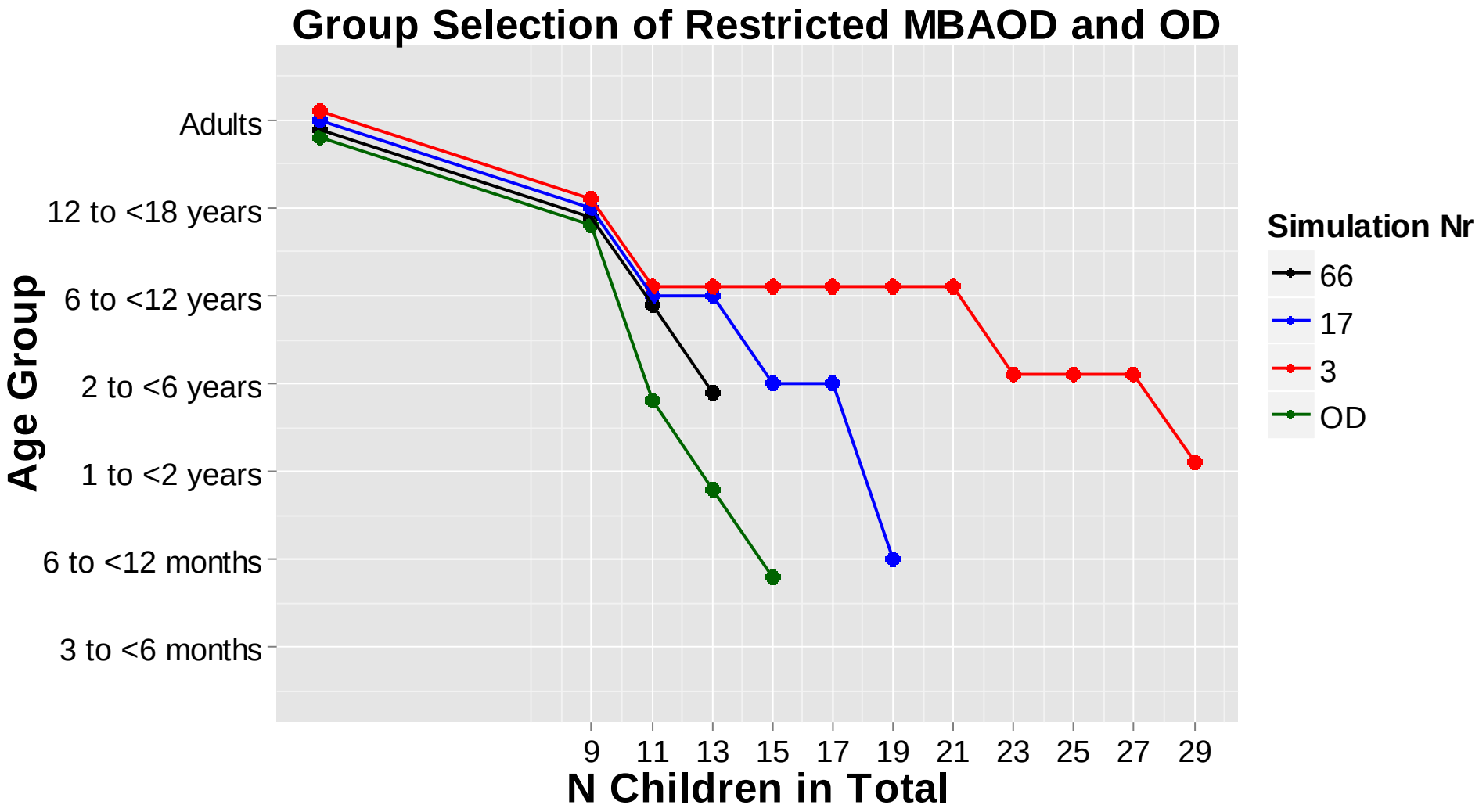

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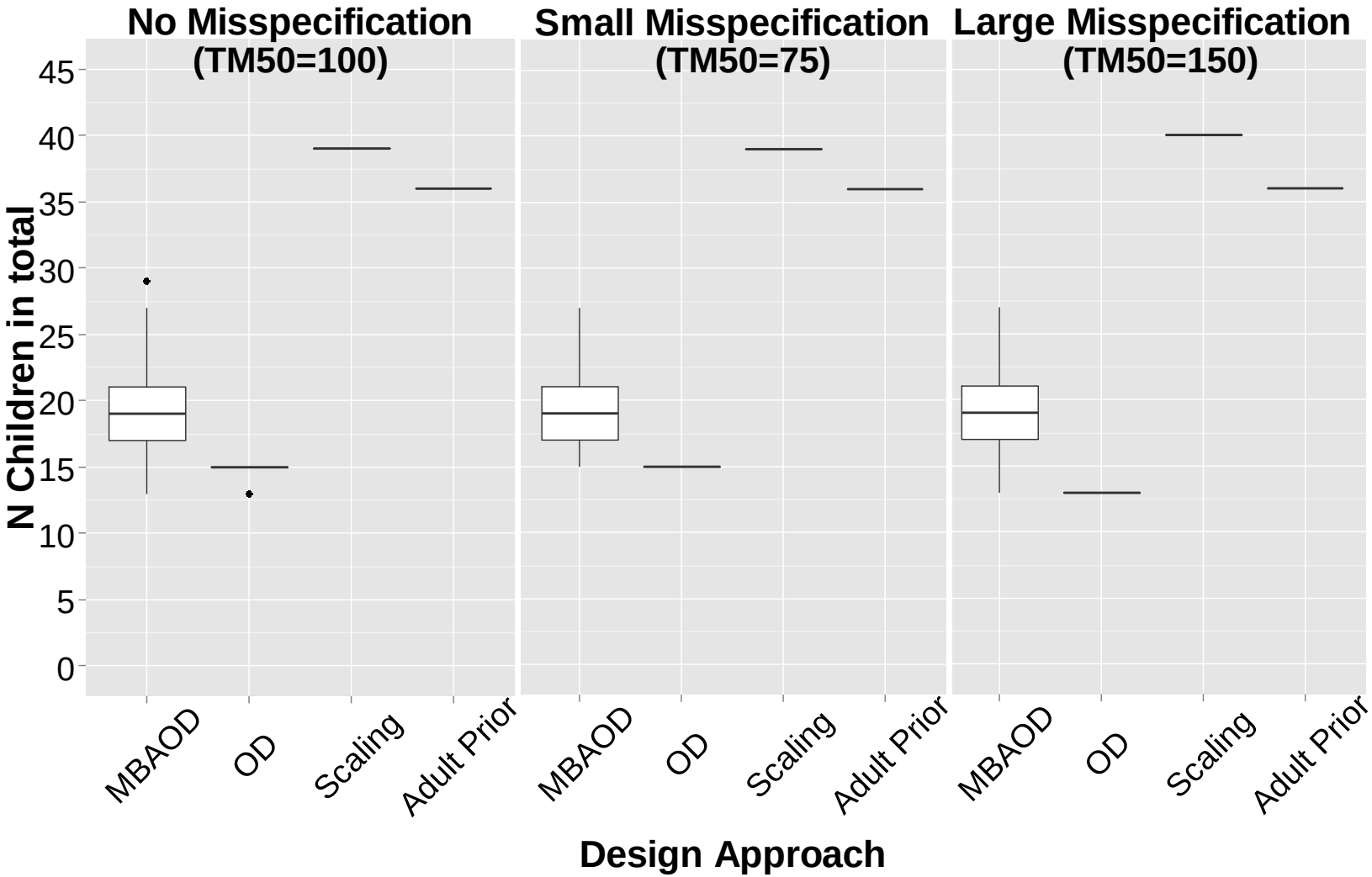
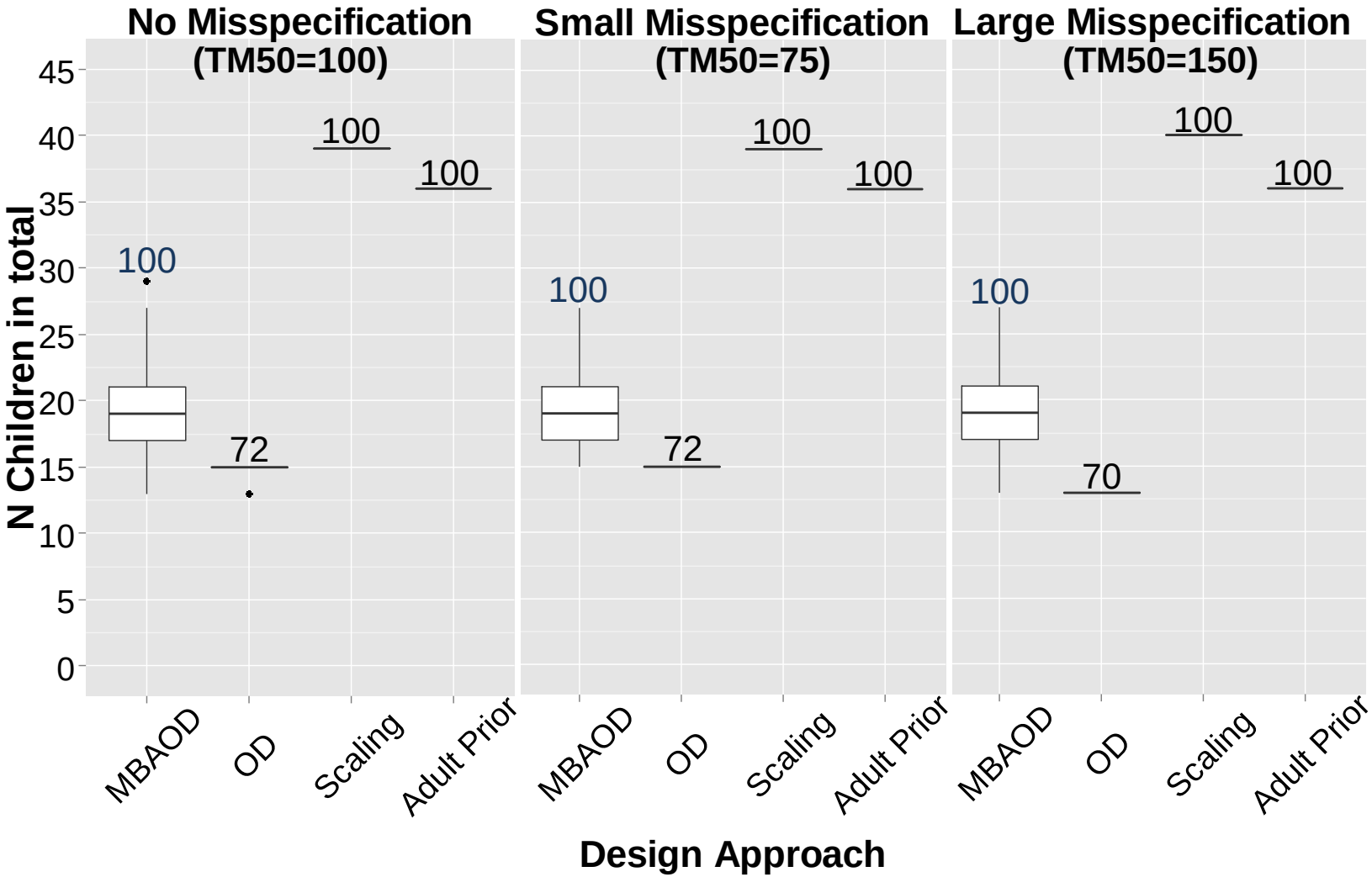
# Results

## Total Number of Children



# Results

## Total Number of Children and Power



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# Conclusions

The FDA precision criteria was successfully 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%

With the stopping criteria itself not being model dependent, any PK or scaling model could be used

# Acknowledgements

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Pharmacometrics Research Group

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Drug Disease Model Resources ddmore

Travel and participation funding:

Apotekarsocieteten

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

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# Extra Slides

# Parameters and Misspecification

| Parameter | Value |
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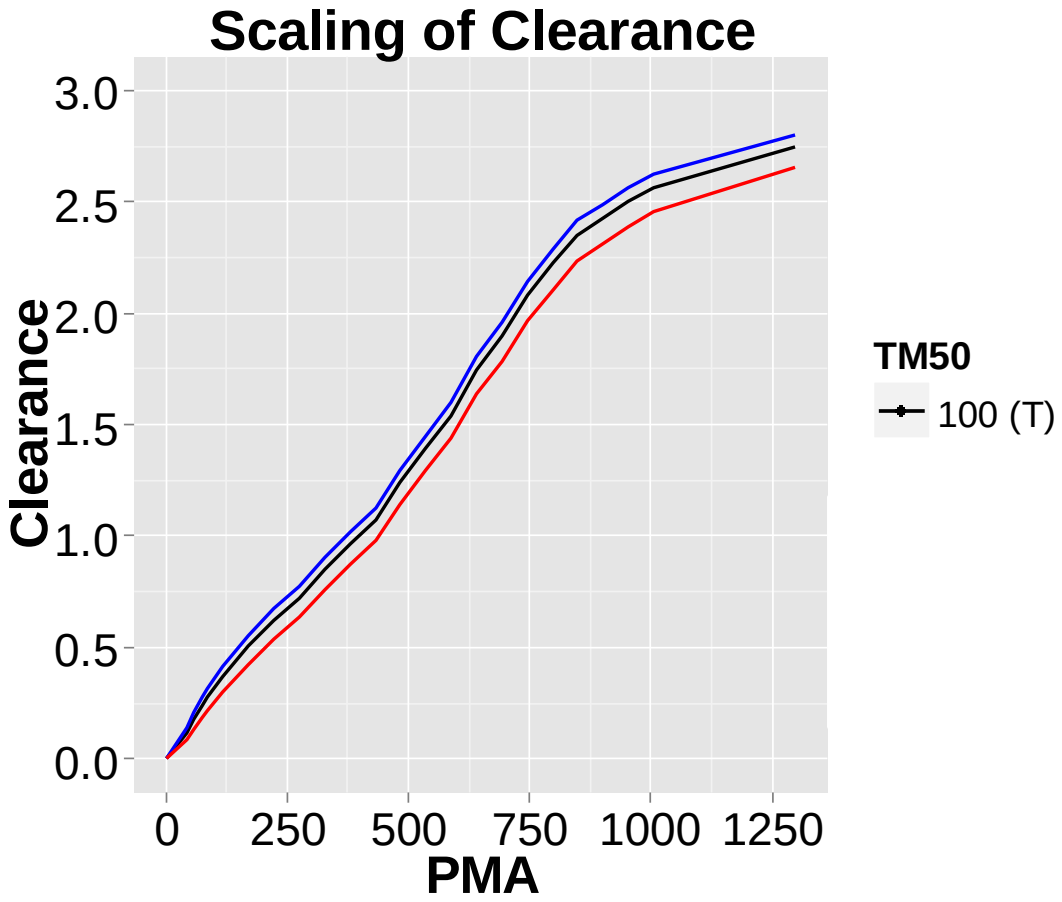

# The Simulated Study Population

| Age Group | Description | Age Range | PMA Range [Weeks] |
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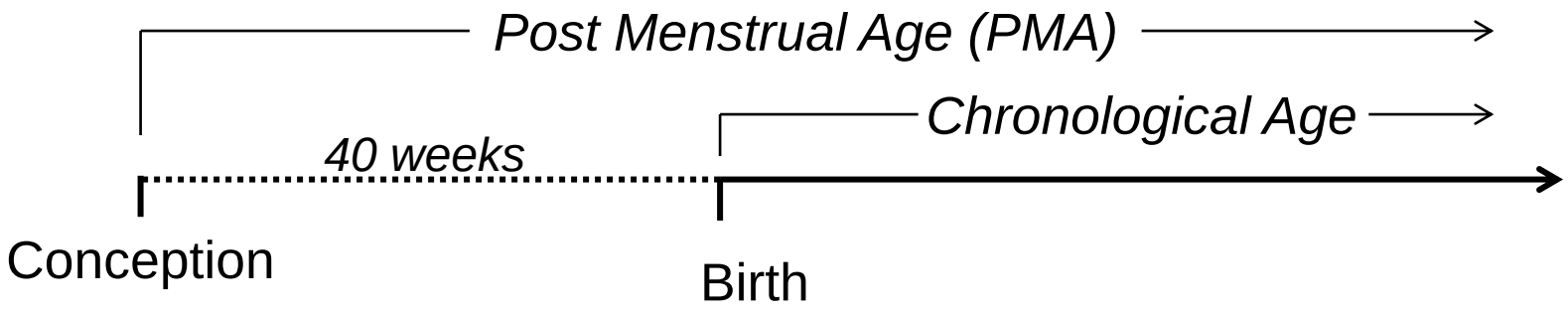
| 2 | Infants | 6 - <12 mo | 66.1 - <92.2 |
| 3 | Toddlers | 1 - < 2 y | 92.2 - <144.4 |
| 4 | Early Childhood | 2 - <6 y | 144.4 - <353.3 |
| 5 | Childhood | 6 - <12 y | 353.3 - <666.5 |
| 6 | Adolescence | 12 - 18 y | 666.5 - <1031.9 |
| 7 | Adults | 20 - 29 y | 1084 - 1553.8 |



# Optimal Design

## Adaptive vs Non-Adaptive

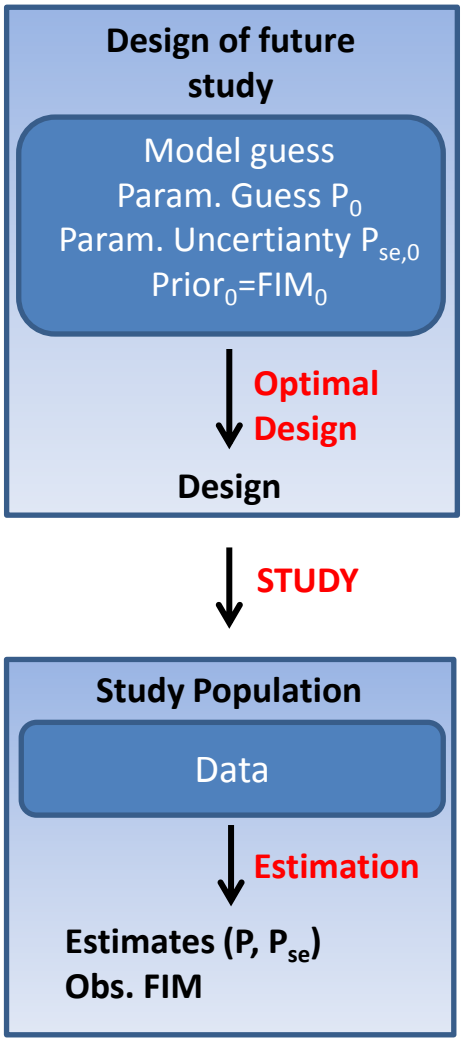
Fisher Information Matrix:

$$FIM = -E_y\left[\frac{\partial^2}{\partial\Theta^2} ln\big(L(\Theta|y)\big)\right]$$

Cramer-Rao inequality:

$$\frac{1}{FIM}(q,\Theta) \leq COV(q,y,\Theta)$$

$y$: Model response
$\Theta$: Model parameters
$q$: Design variables



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# Expandability
## and future work

Implement a library of scaling models

Implement functionality for model averaging and model discrimination.

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# Optimal Design

## Adaptive vs Non-Adaptive