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Platform for adaptive optimal design of nonlinear mixed effect models

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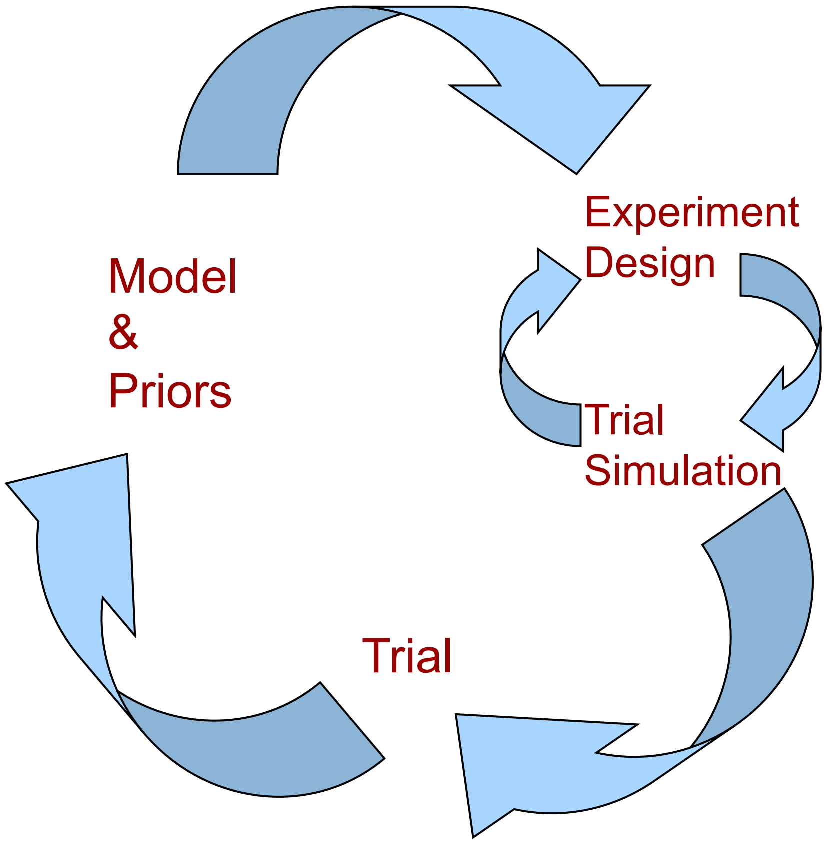
Model based drug development



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Outline

- Robust optimal design
- Adaptive optimal design (AOD)
- Platform for testing and performing AOD trials (DDMORE)
- Exploring AOD
  - Pediatric bridging studies (PK)

Robust optimal design

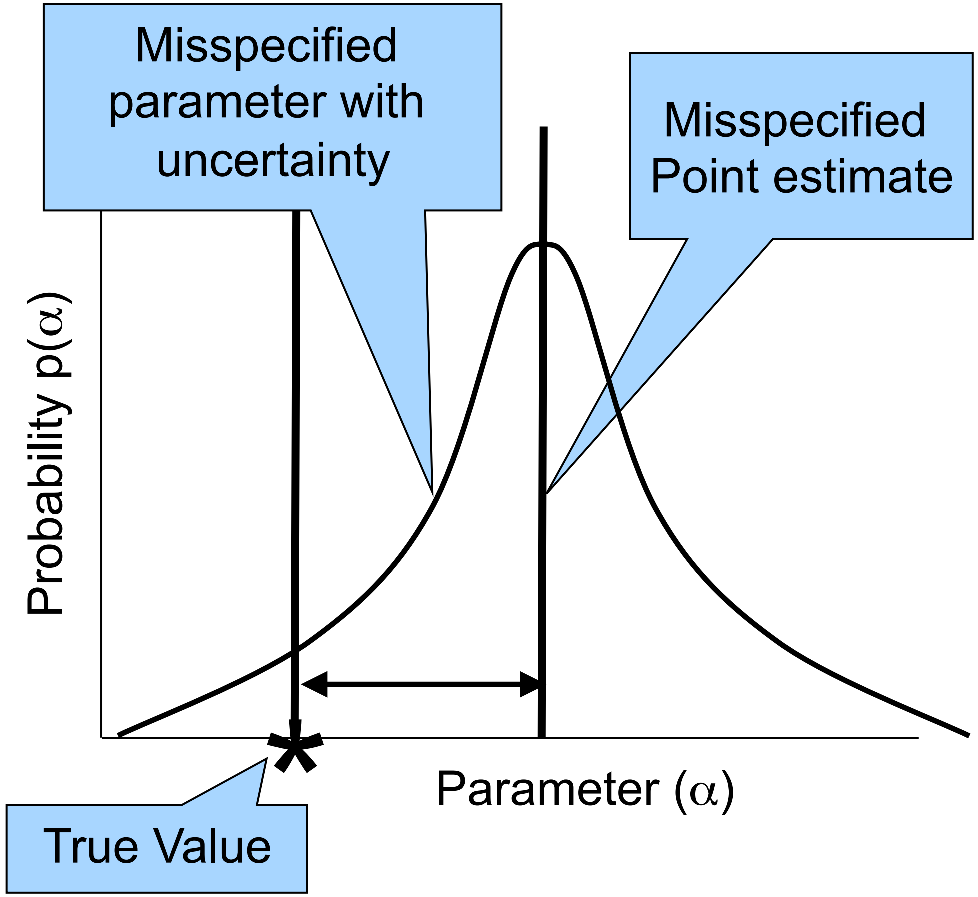
- Standard optimal design requires knowledge about the underlying model and parameter values for that model

$$FIM(\text{models}_{fixed}, \text{parameters}_{fixed}, \text{design})$$

- **What if we don't know the model or we don't have a good guess for the parameters of a model?**

Robust optimal design (2)

- Assume your parameters have distributions
  - ("E-family", e.g. ElnD)
- Problems if:
  - Distribution does not overlap the true value
  - One region of parameter values "drive" the design



M.G. Dodds, A. Hooker and P. Vicini. *J Pharmacokinet Pharmacodyn*, 32(1):33-64, 2005.

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Robust optimal design (3)

- Incorporate multiple models into your optimization

$$\Psi_{P-D} = \arg\max_{\xi}\left(\sum_{i}^{m}\log\left(|FIM(\xi,\Phi^{\{i\}})|^{\frac{\alpha_i}{p_i}}\right)\right)$$

m=model #, α_I = weighting and $p_i = \#$ of parameters

- Problems if:
  - "true" model is not one of the candidate models.
  - Parameters are not near the "truth"

Hooker and Vicini, J. AAPS, 2005
Waterhouse and Duffull, JPKPD, 2005

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Problems with robust design

- If you have too much uncertainty or too many potential models:
  - Rich design covering entire design space is needed

- Are there other ways to deal with uncertainty?

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Adaptive Optimal Designs (AOD)

- Another type of robust design

- Adapt and update your understanding of the system (the model) at intermediate steps within a trial, then re-optimize

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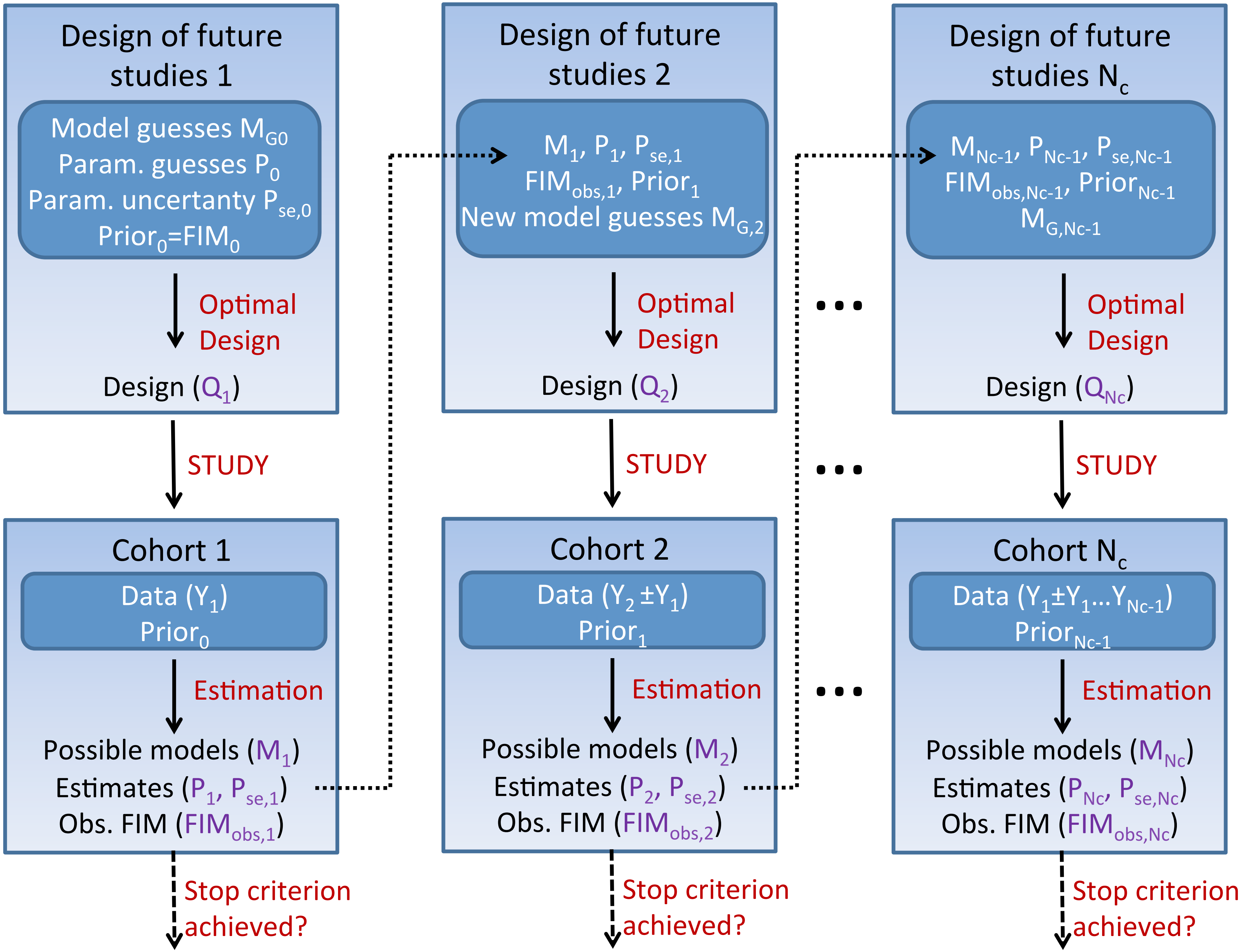
Some previous work with AOD

- A recent survey has found that for 10 European pharmaceutical companies the importance of AOD for NLMEM was ranked, on average, 4 on a scale of 5 (Mentre et al. CPT:PSP, 2013).
- Previous work has demonstrated the usefulness of AOD in
  - PET occupancy studies (Zamuner et al. CPT, 2010).
  - bridging studies (Foo and Duffull. Pharm. Res., 2012).
  - population PK in children (Dumont et al. PAGE, 2012).



Design of future studies 1
Model guesses M_{G0}
Param. guesses P_0
Param. uncertanty $P_{se,0}$
$Prior_0=FIM_0$
Optimal Design
Design (Q_1)
STUDY
Cohort 1
Data (Y_1)
$Prior_0$
Estimation
Possible models (M_1)
Estimates (P_1, $P_{se,1}$)
Obs. FIM ($FIM_{obs,1}$)
Stop criterion achieved?
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AOD the good and the bad

- Good
  - Allows for adjustment of uncertainty in models and parameters
  - Adjustment in misspecification if present
- Bad
  - If you are not wrong from the beginning then adaptations may just introduce error.
  - Adjustments being driven by a small group of patients…may lead to bias.

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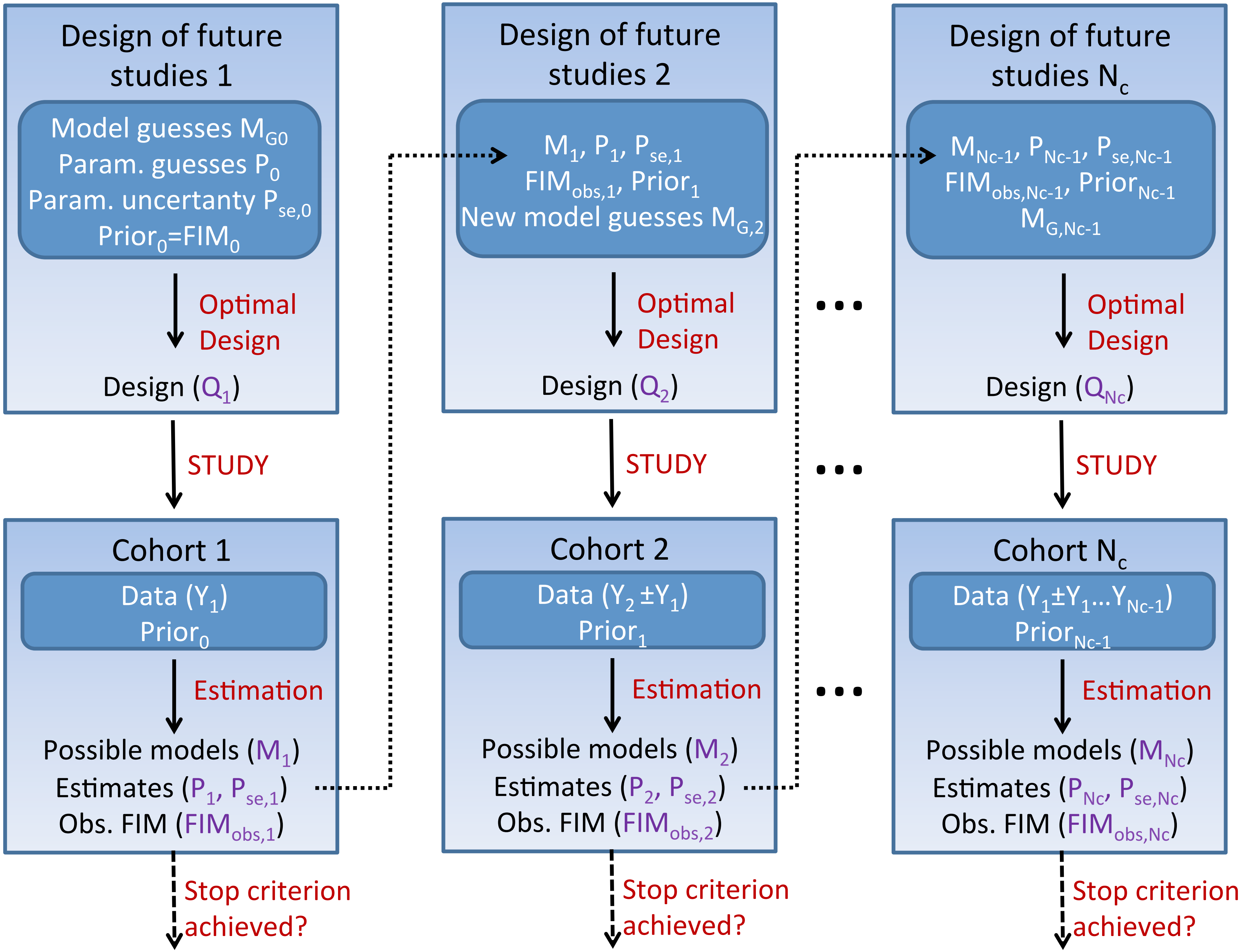
PLATFORM FOR TESTING AND PERFORMING AOD TRIALS (DDMORE)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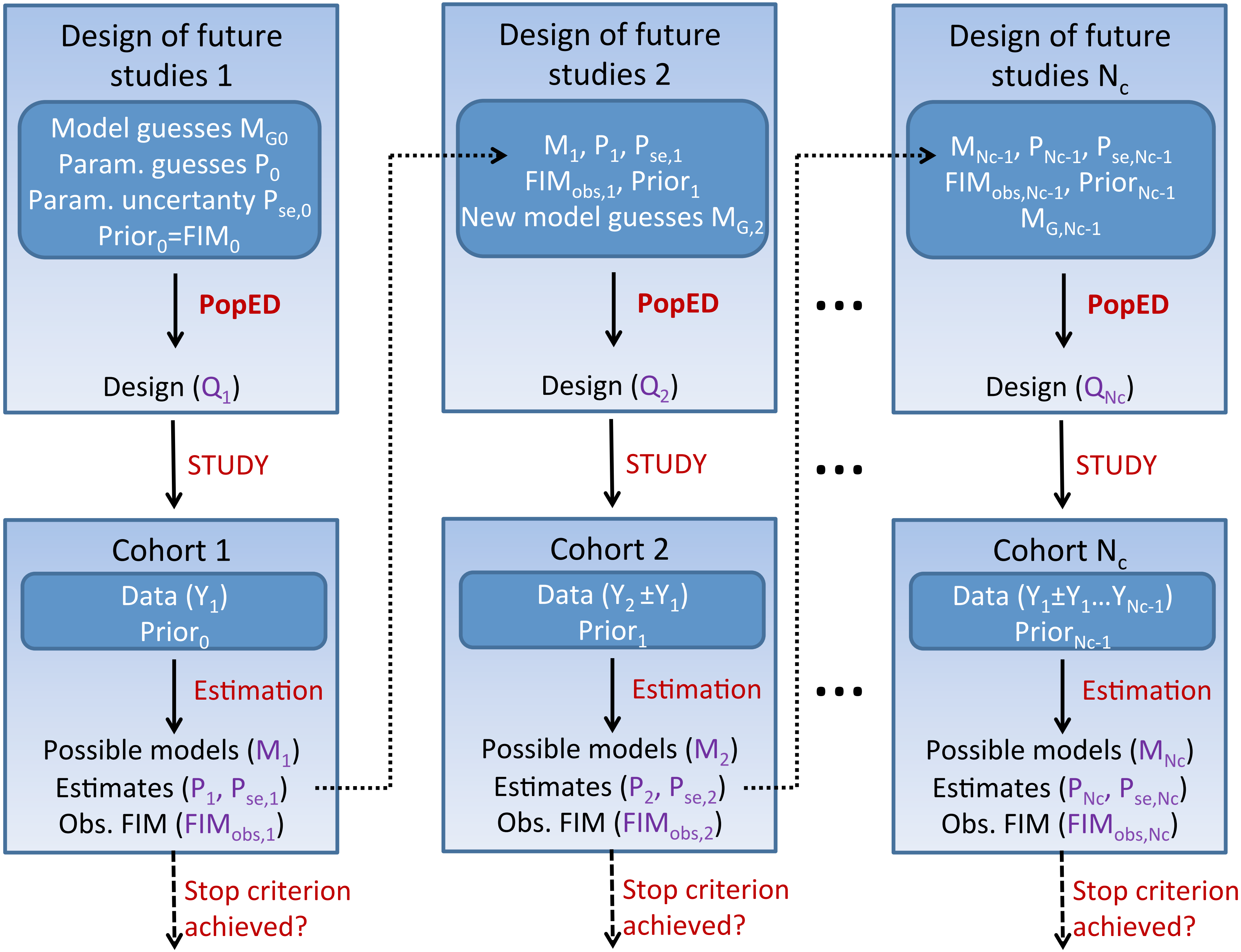
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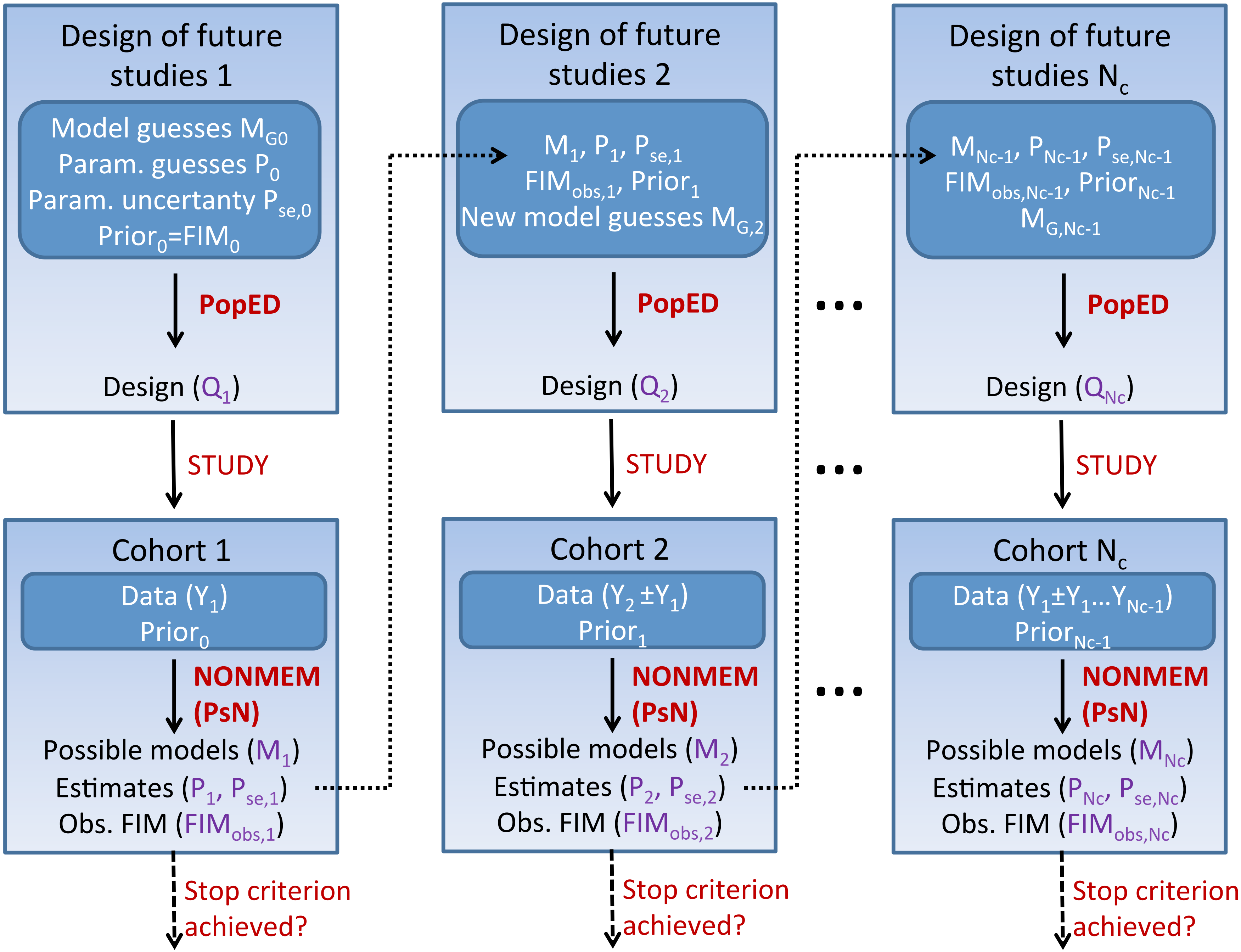

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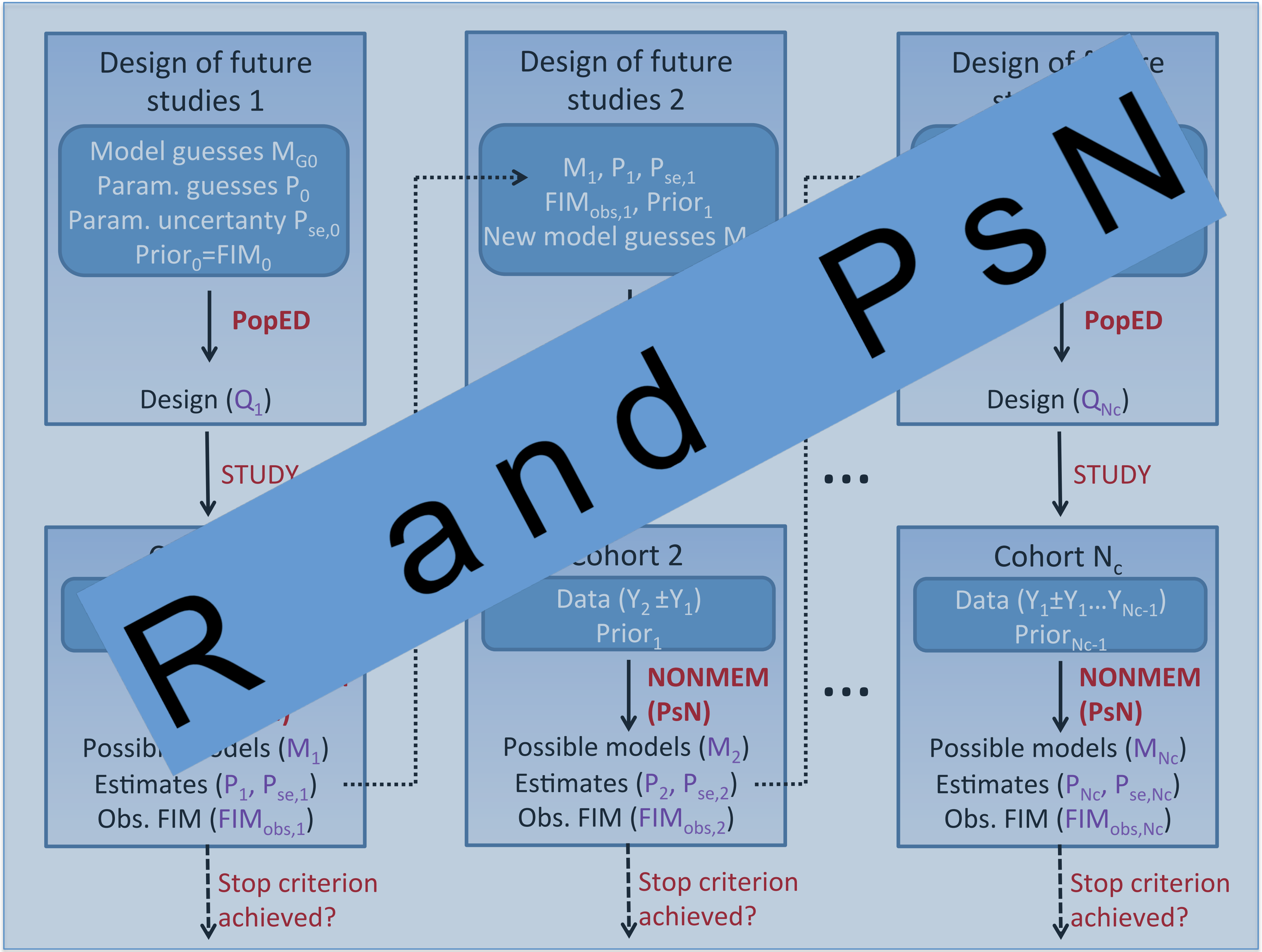

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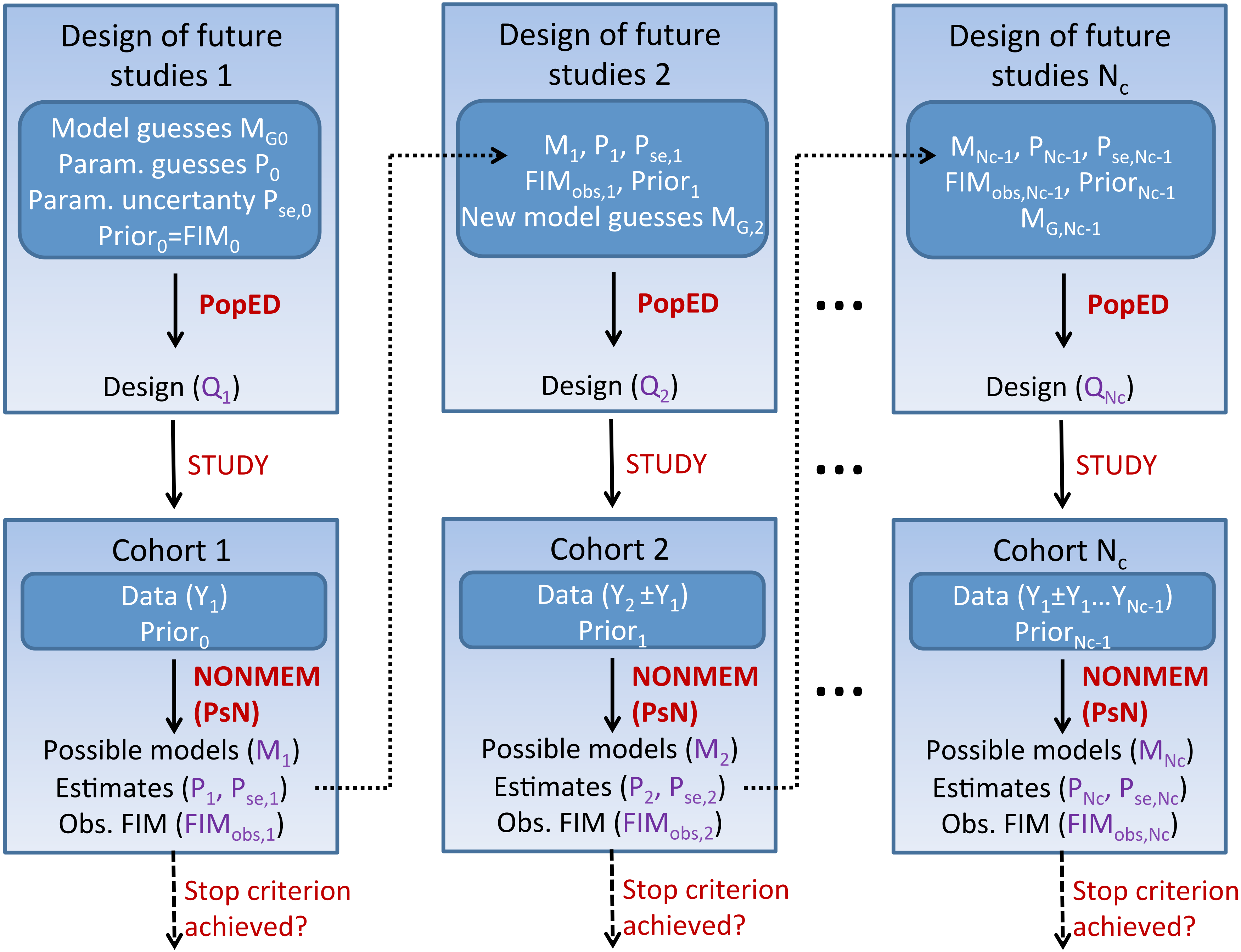

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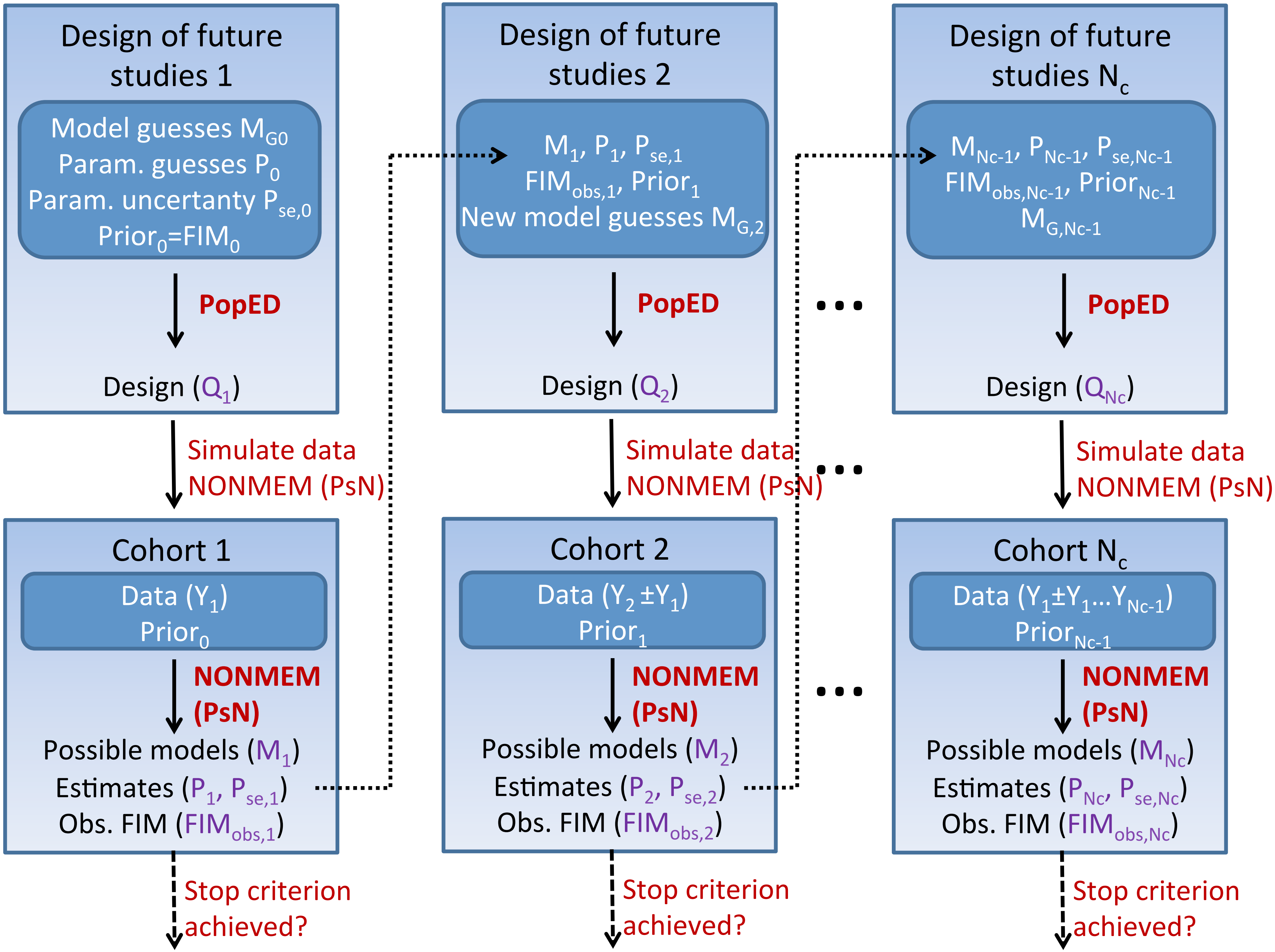

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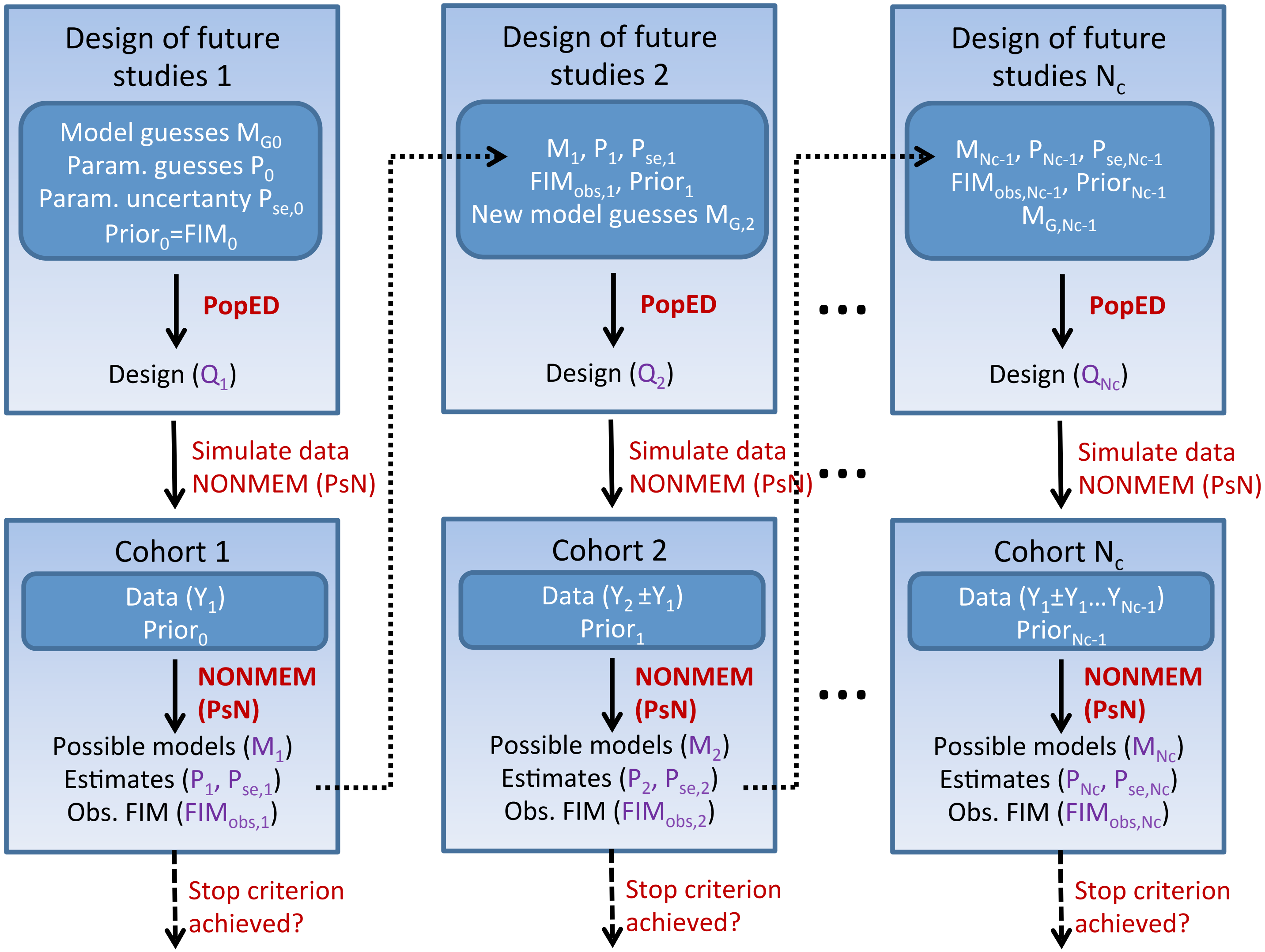
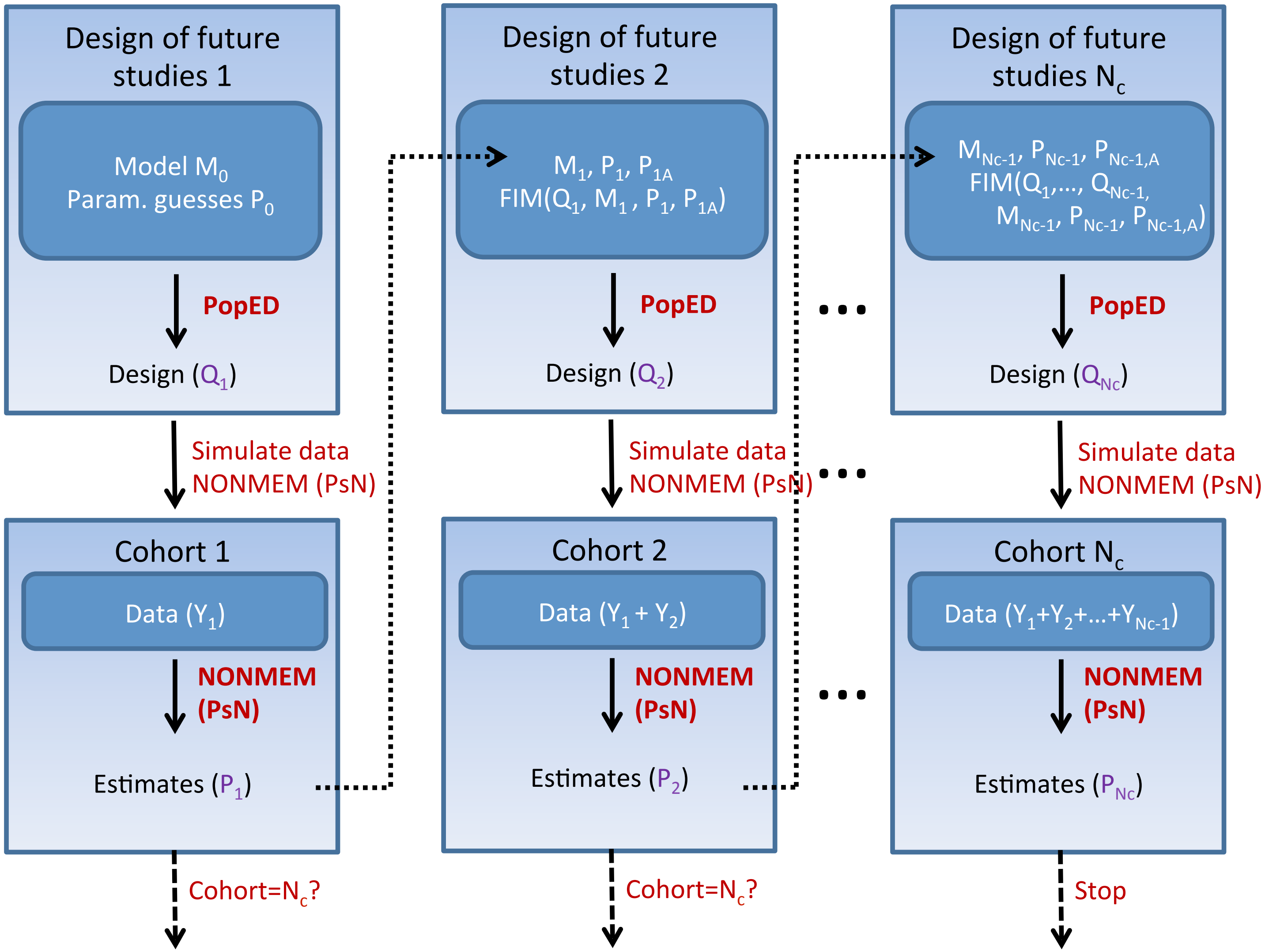
Evaluating AODs – Multiple simulations

- Simulate entire process many times (R and PsN)
- Evaluate results in some way (R and PsN)



For the coming example

- Simulate entire process many times (R and PsN)
- Evaluate results in some way (R and PsN)



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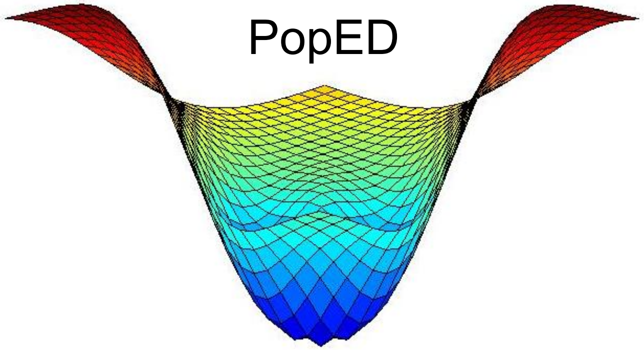

poped.sf.net

- Optimal experimental design software
- Flexible description of models
- Flexible description of design space
- Flexible design optimization
- Written in Matlab

PsN3
Perl speaks NONMEM

psn.sf.net

- Perl Speaks NONMEM
- Aids in running nonmem
- Automatic evaluation of complex statistical techniques
- Extraction of important results from NONMEM

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AOD prototype

- Modular so that the calls to PopED, PsN and NONMEM can be switched out for other programs.
- General so that “any” model (and adaptation) can be used.
- DDMoRe (www.ddmore.eu)
  - Platform for AOD
  - Investigate optimal strategies for AOD

Van Hasselt and Hooker, PAGE, 2013

Veronese et al. AODware: a model-based application for optimal and adaptive optimal experimental design exploration, ACOP, 2013

Exploring AOD – Pediatric PK bridging studies

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- Several model types to describe PK changes in children
  - Empirical: $$CL_i = CL_{std,i} \cdot \left(\frac{WT_i}{70}\right)^{\theta} \cdot \ldots$$
  - Holfordian: $$CL_i = CL_{std,i} \cdot \left(\frac{WT_i}{70}\right)^{0.75} \cdot \frac{PMA_i^{\gamma}}{PMA_i^{\gamma} + TM_{50}^{\gamma}} \cdot F_{organ,i} \cdots$$
  - PBPK …

Anderson and Holford. “Tips and traps analyzing pediatric PK data.” Pediatric Anethesia, 2011.

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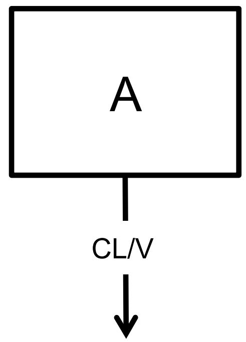
Pediatric PK bridging study

- For this example we chose a somewhat simplistic approach:

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



$$CL_i = CL_{BASE,i} + \frac{CL_{MAX} \cdot WT_i^{\gamma}}{WT50^{\gamma} + WT_i^{\gamma}}$$

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

$$CL_{BASE,i},\ V_{STD,i} \in LogNormal$$

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

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Pediatric bridging study

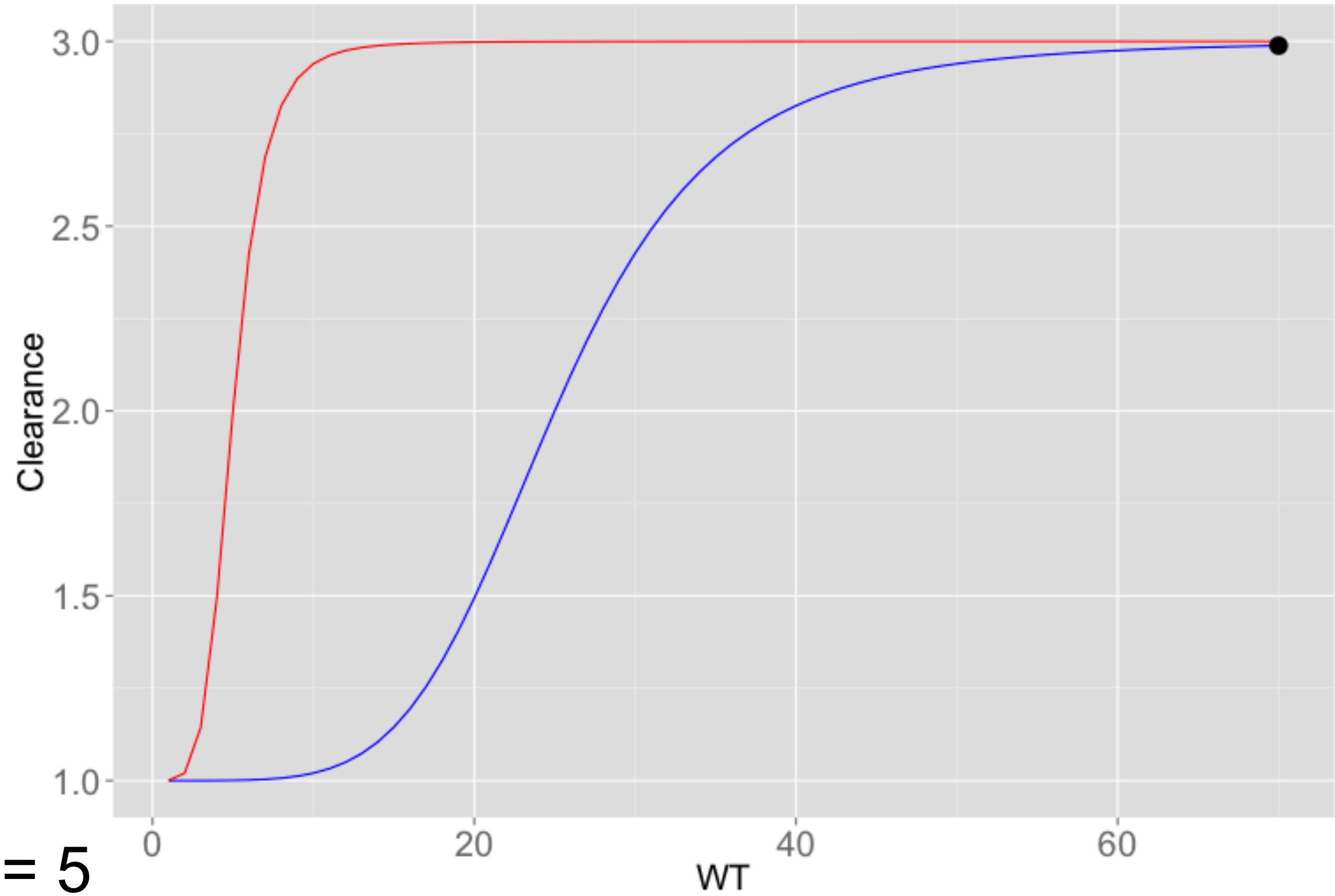
- Cohorts optimized on
  - Weights to include in cohort
  - Sampling times.

- Compared the performance of two study design approaches:
  - Fixed optimized design (D-optimal)
  - Adaptive optimized designs (D-optimal).

- For each design approach we evaluated:
  - Different levels of parameter misspecification

- The resulting study designs were evaluated based on:
  - Parameter bias and precision
  - Predicted exposure (AUC).

Fixed D-optimal design with misspecification of WT50



Prior: WT50 = 5
Truth: WT50 = 25

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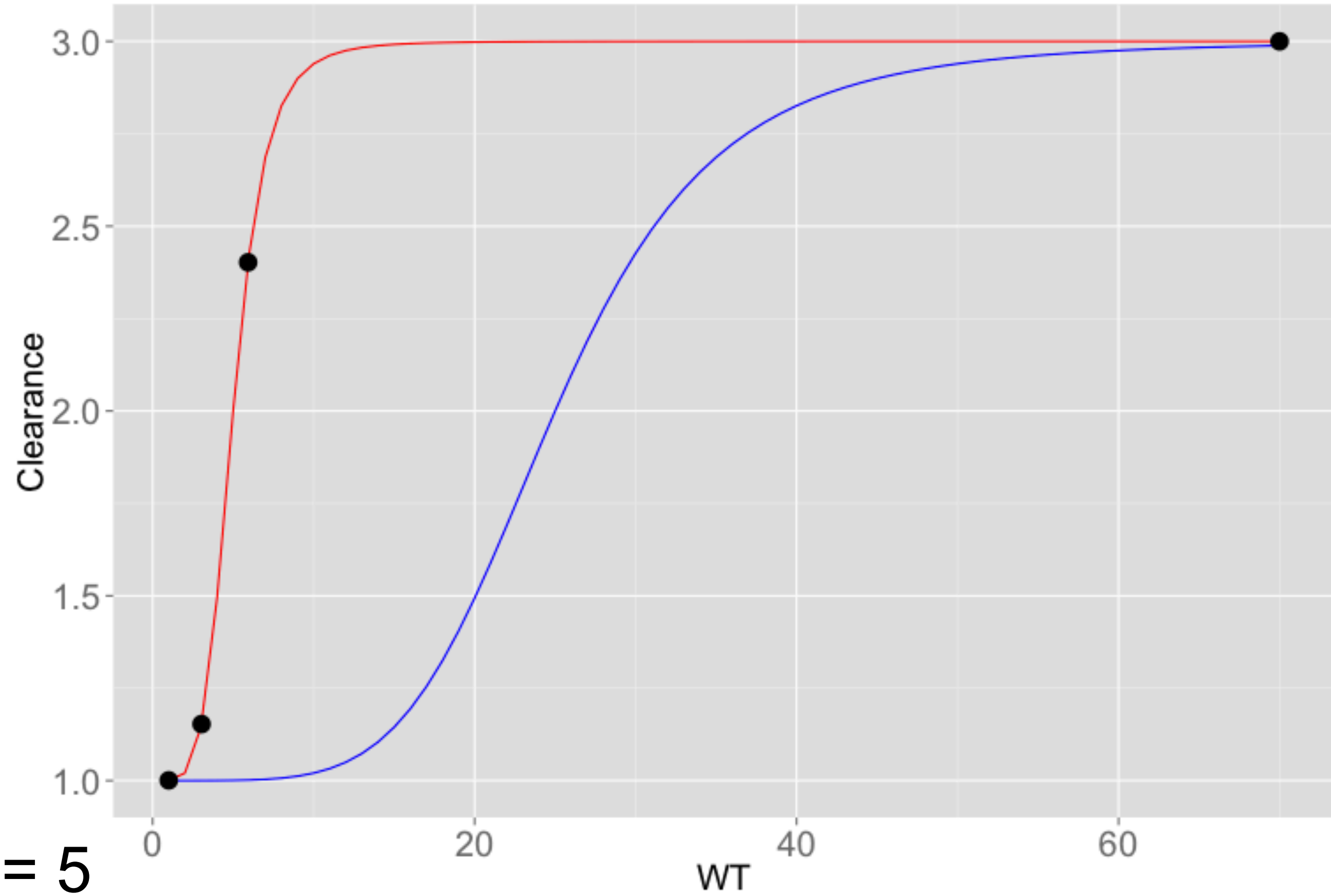
Fixed D-optimal design with misspecification of WT50



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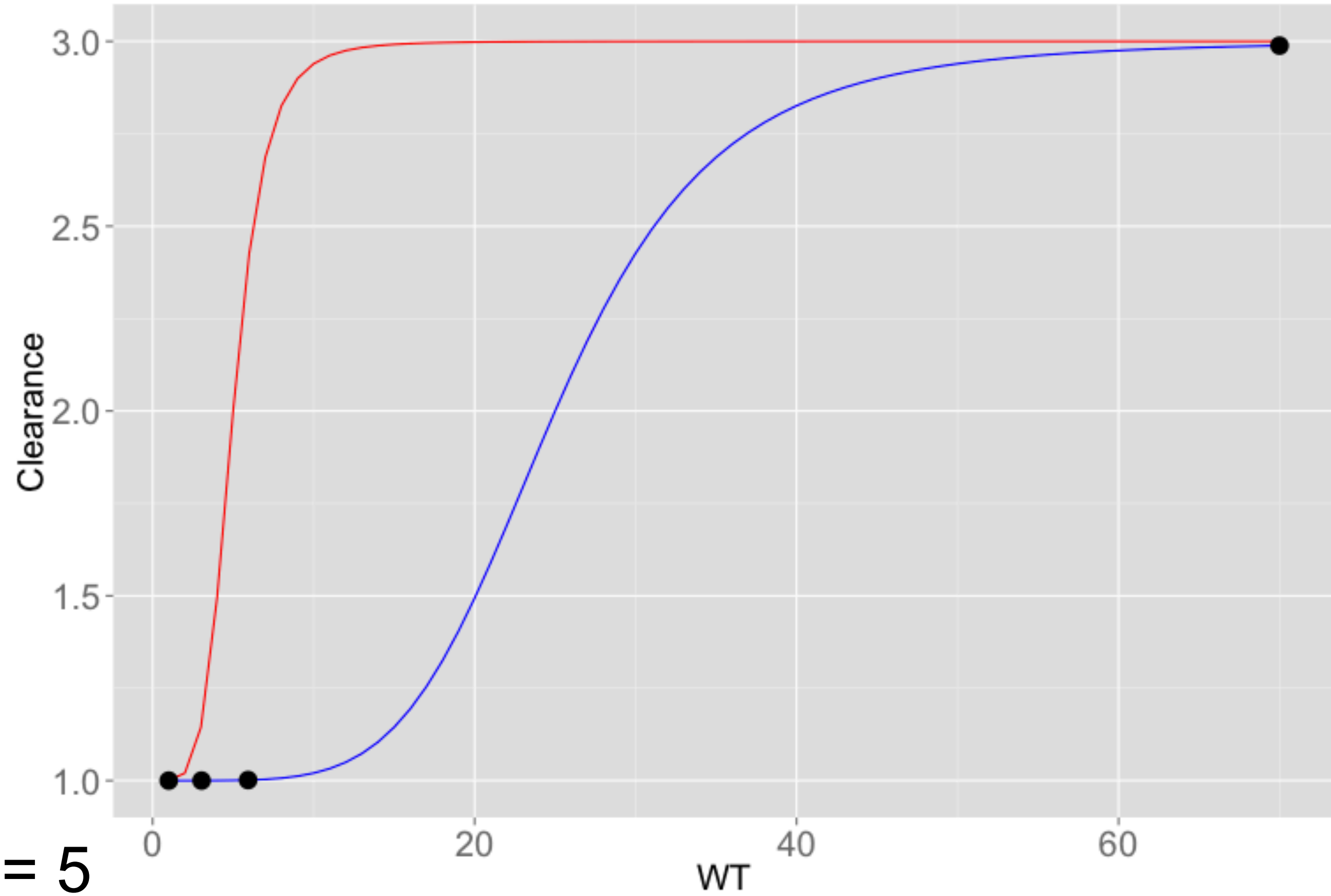

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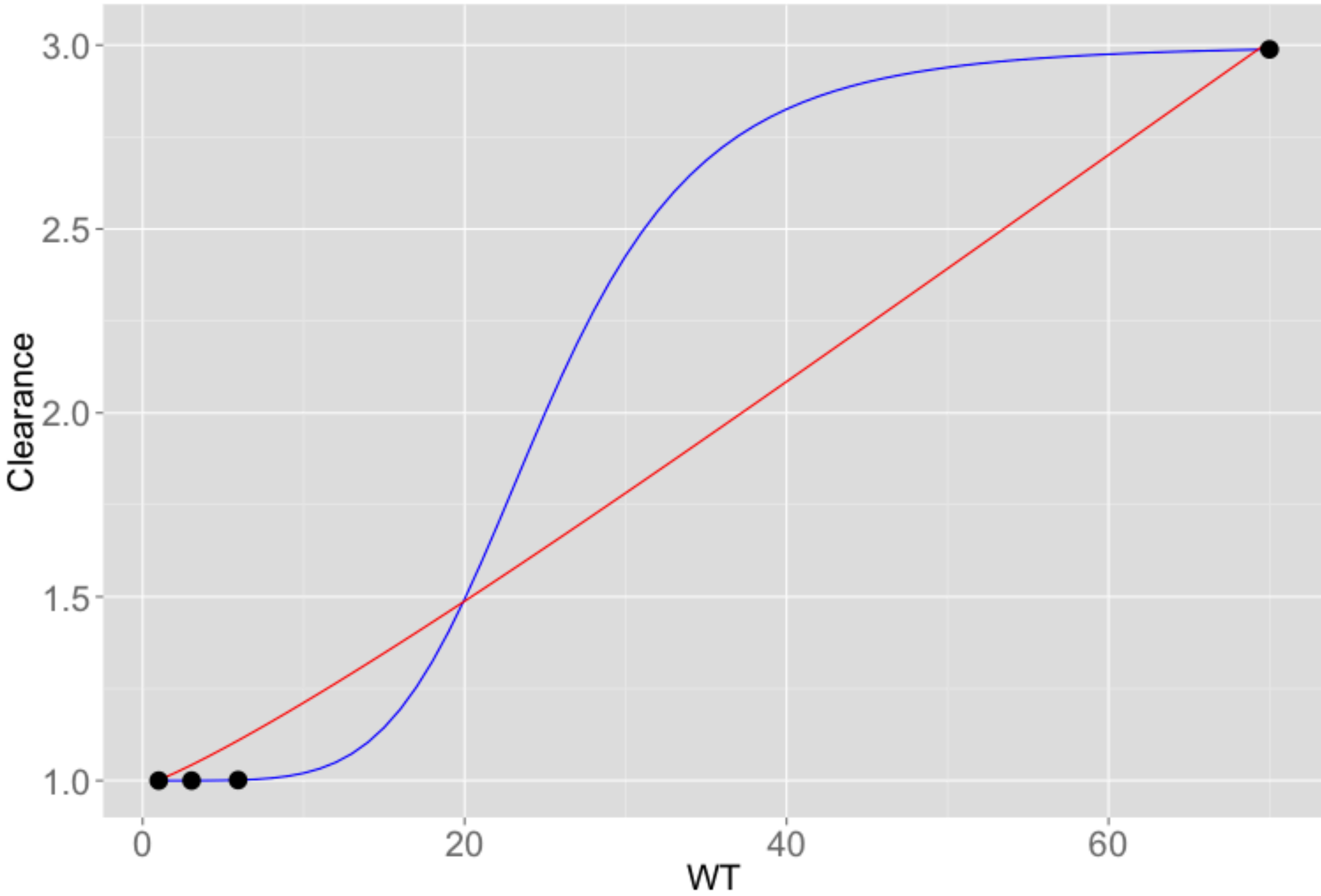

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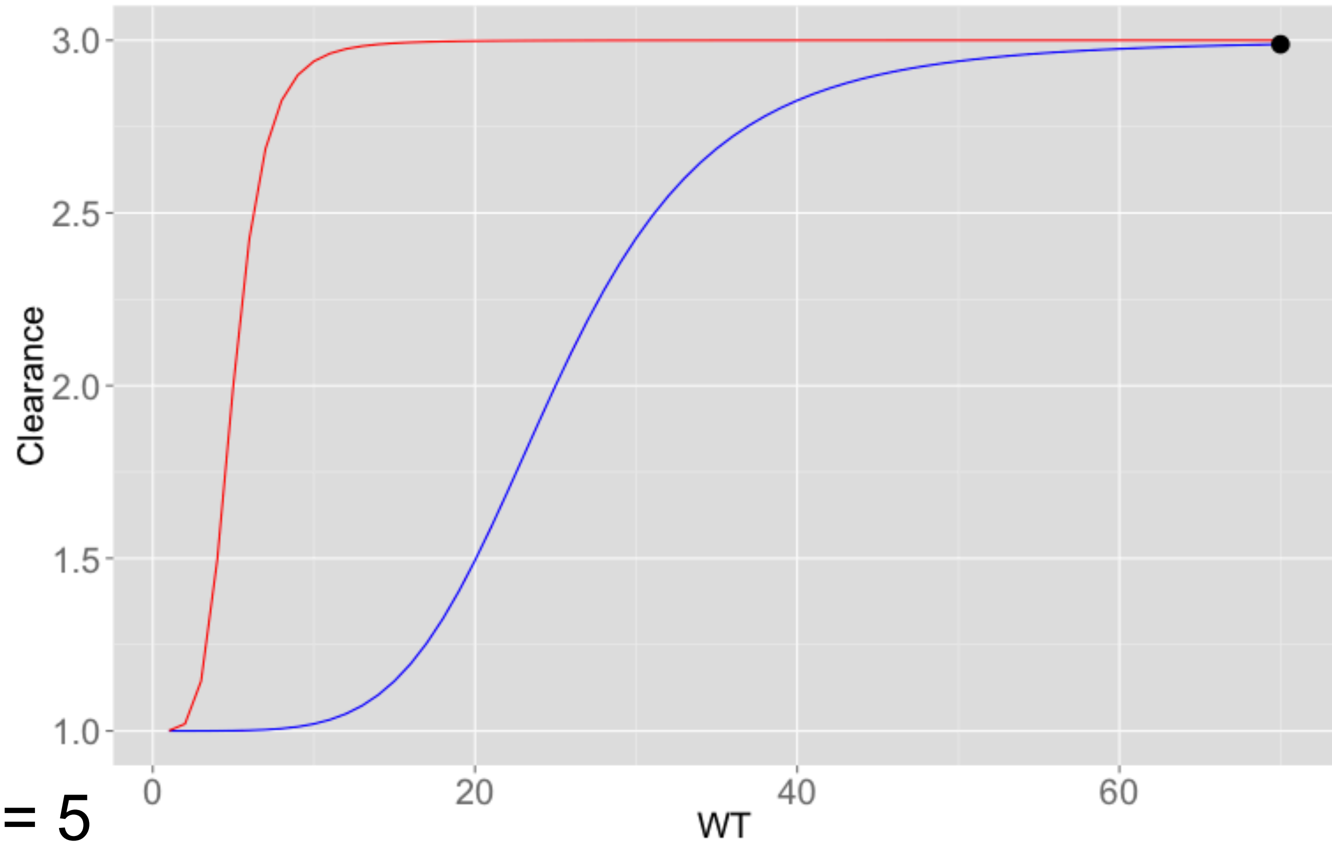
Adaptive D-optimal design with misspecification of WT50



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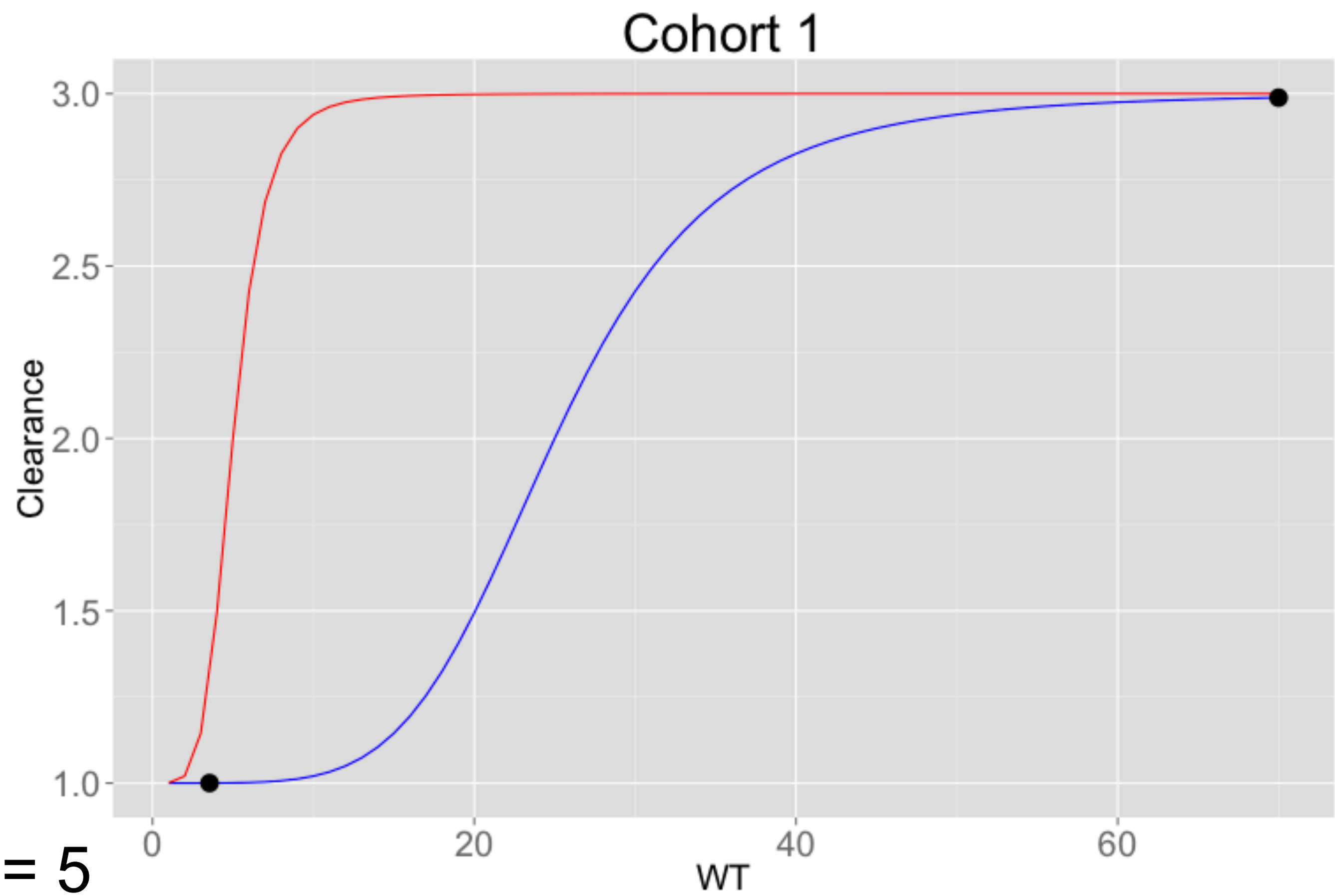

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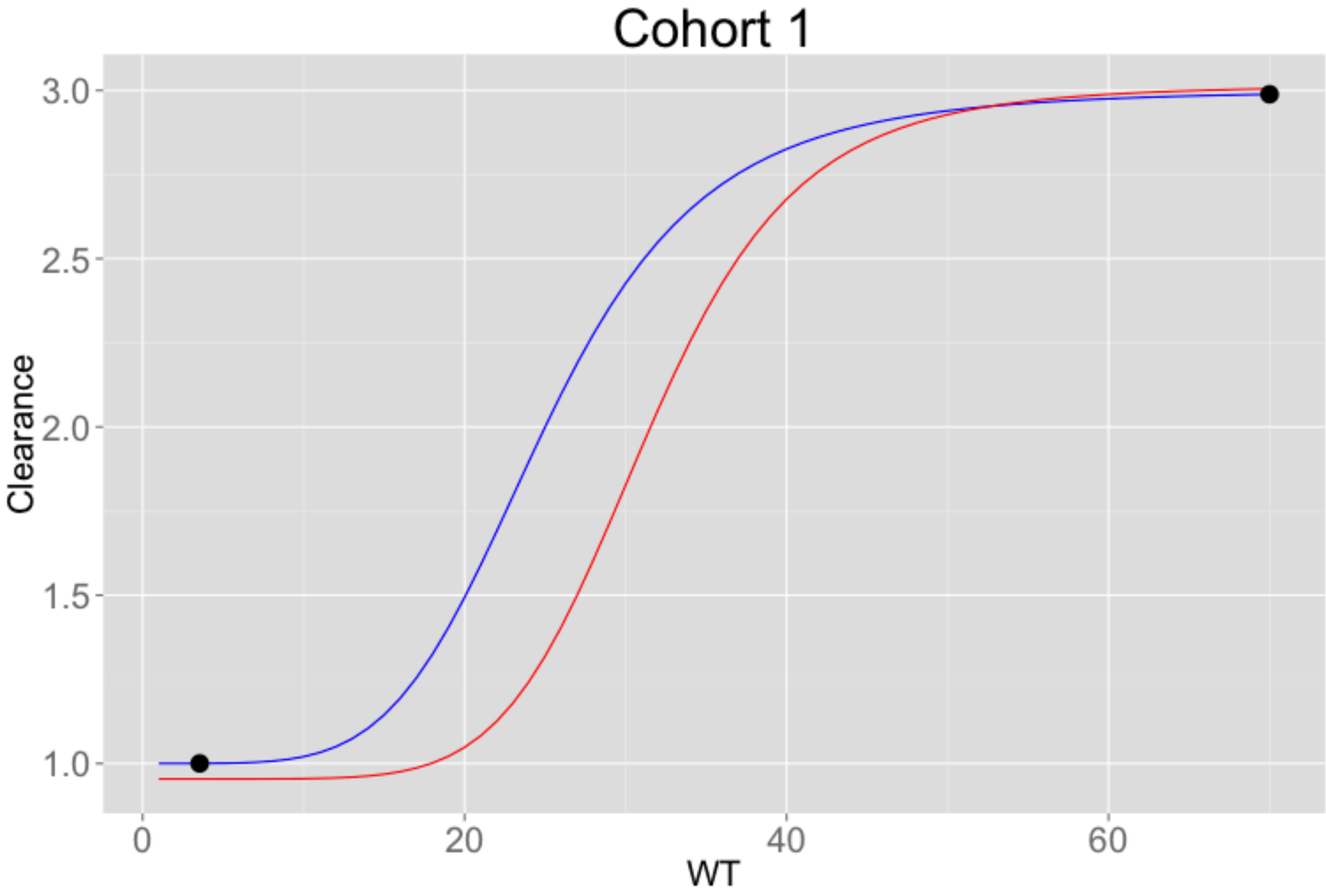

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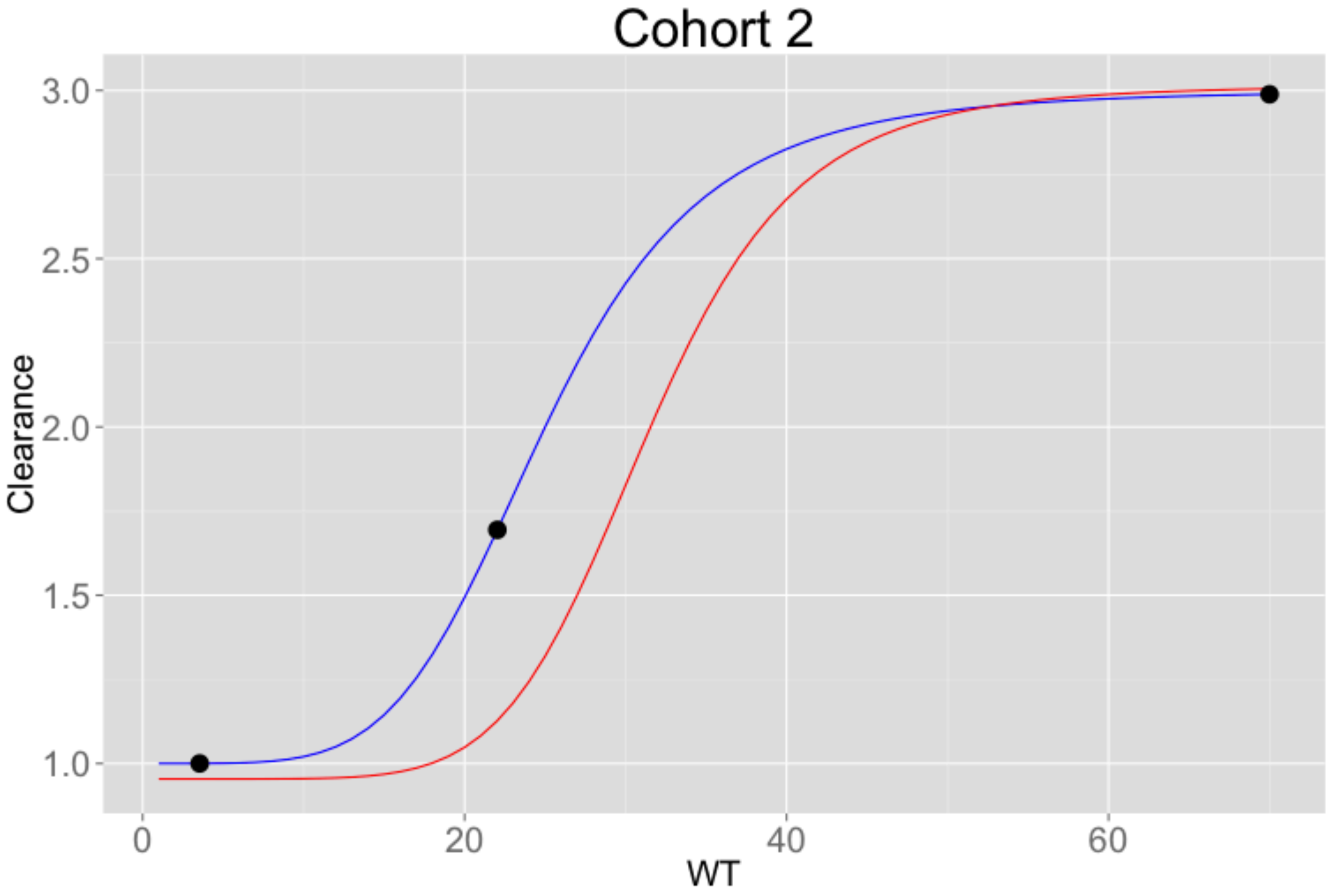

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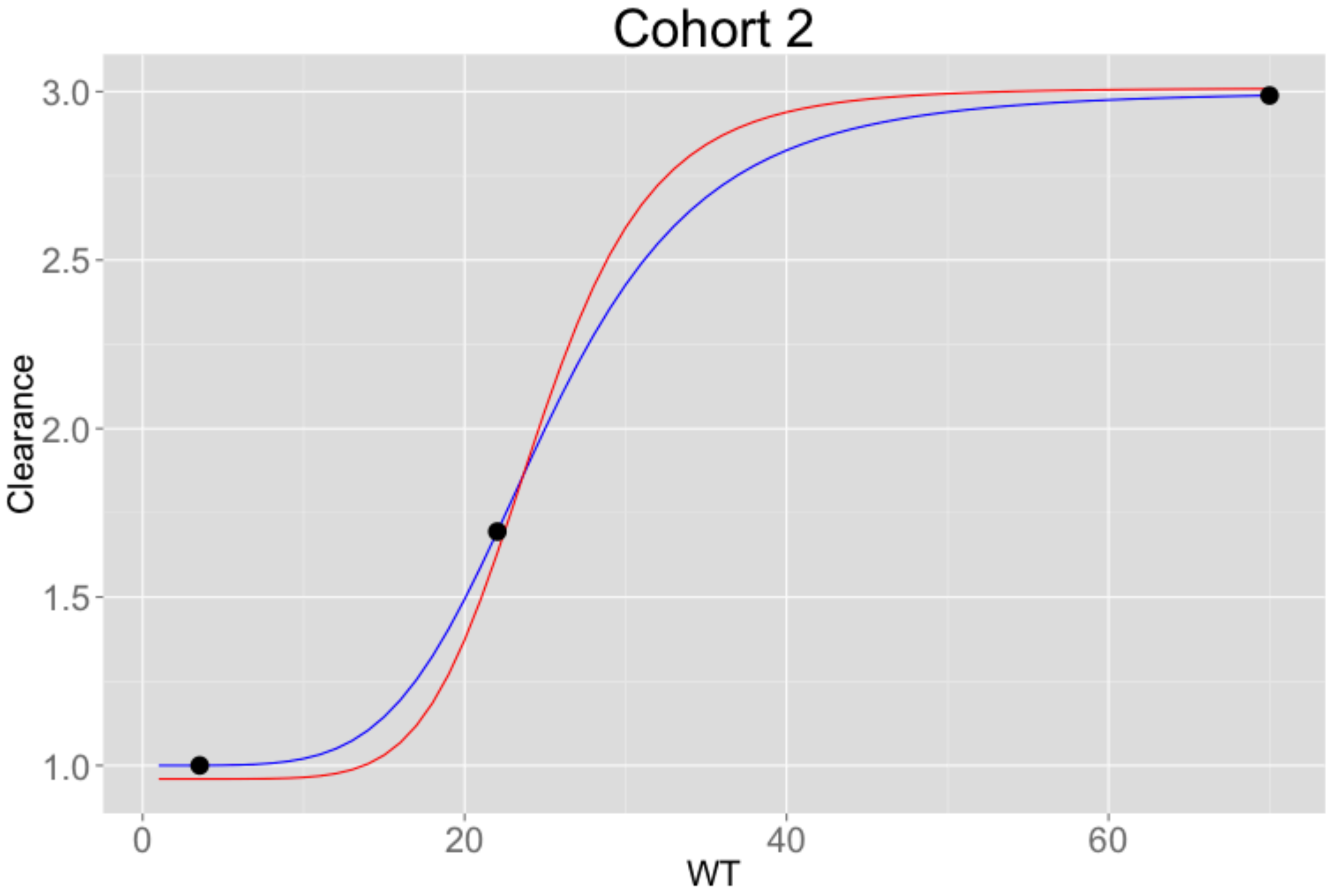

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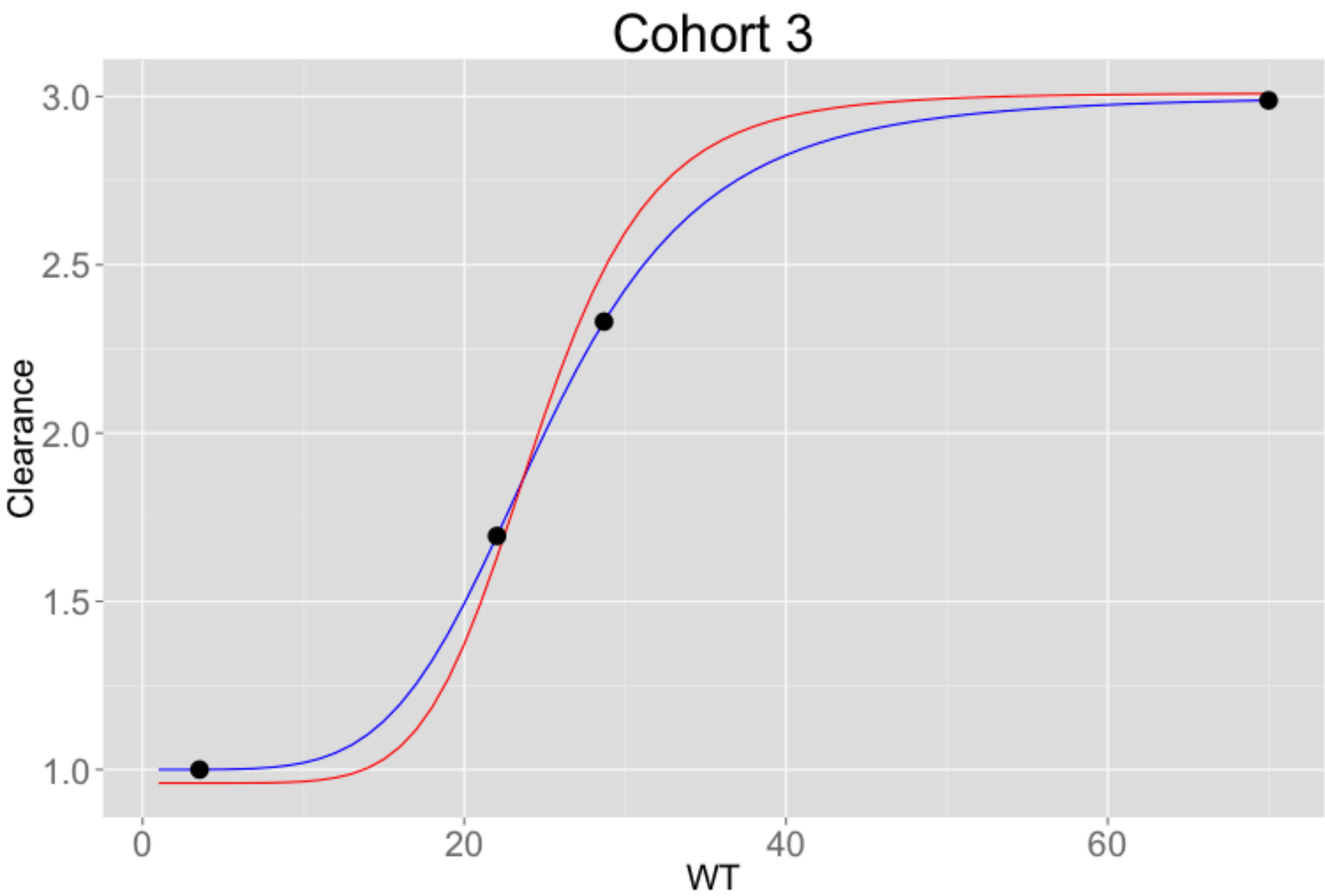

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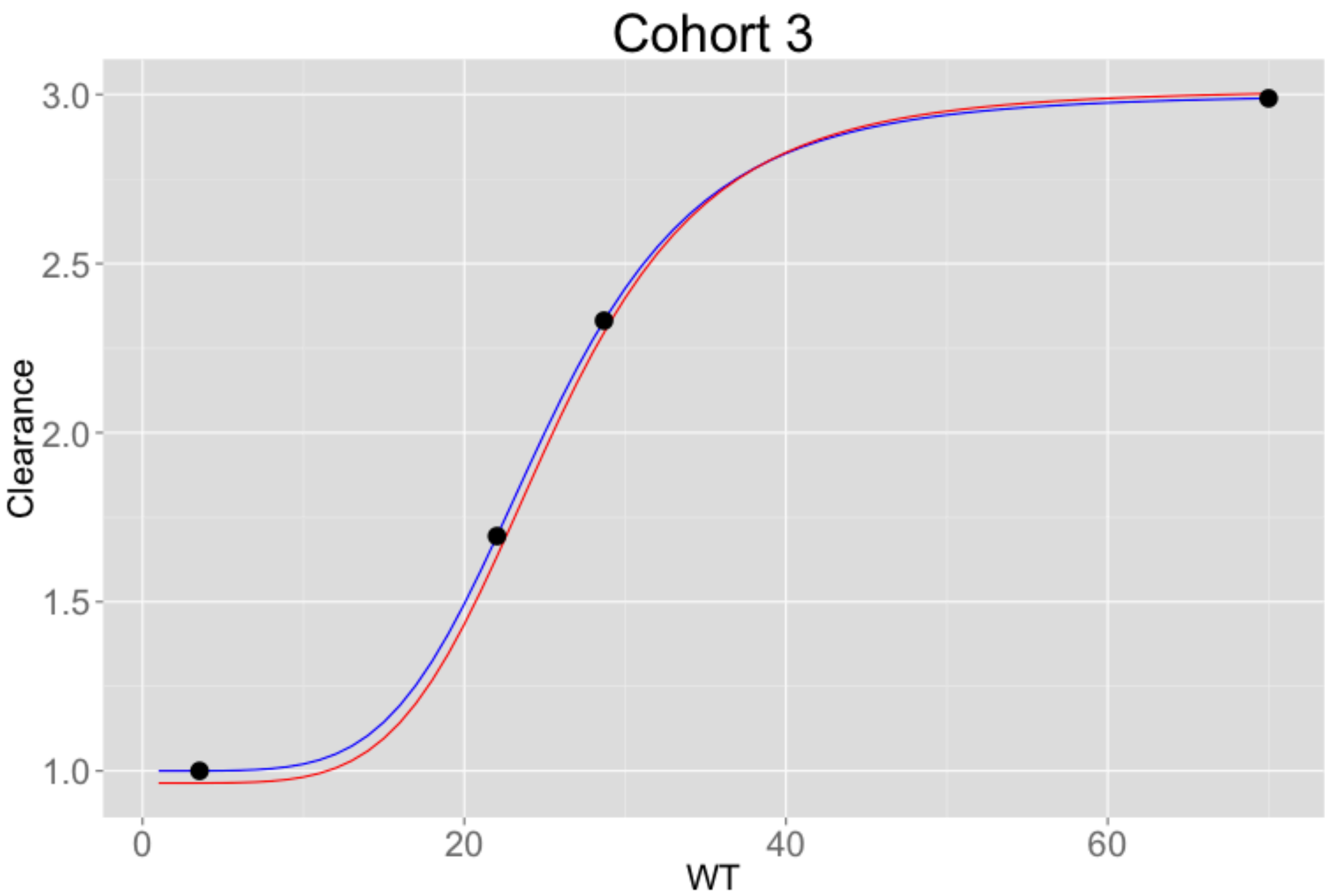

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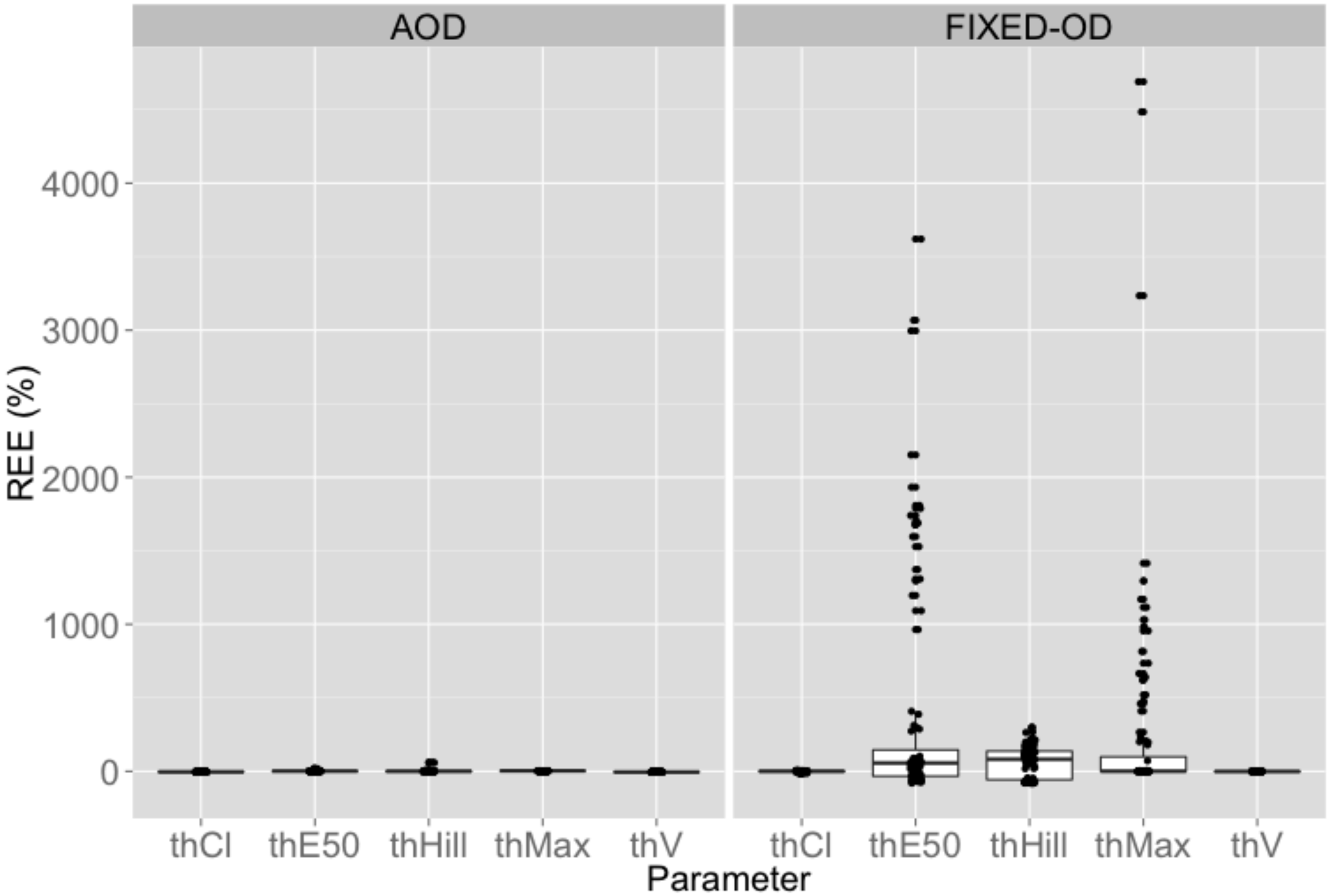
REE (%) of Parameter estimates



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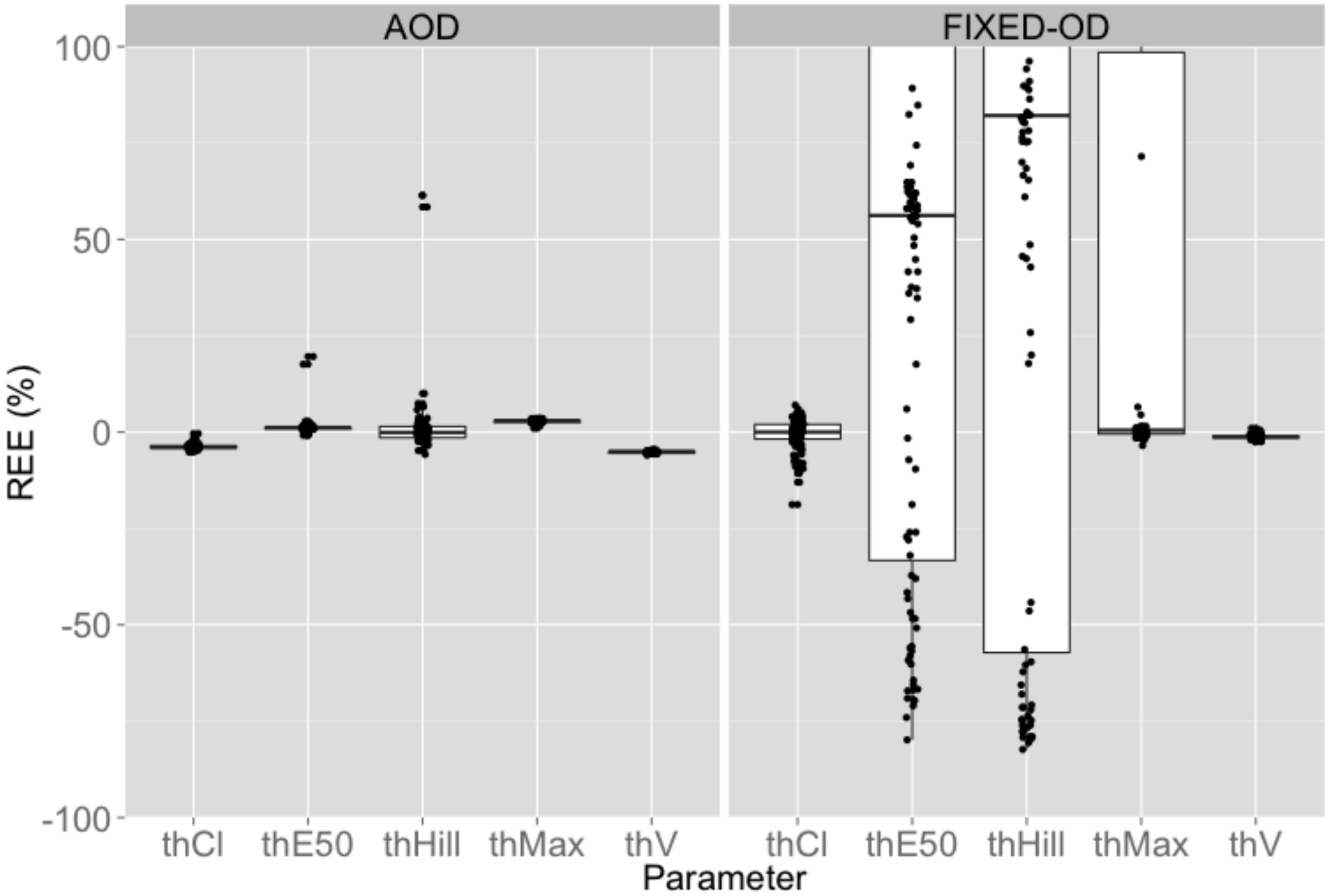
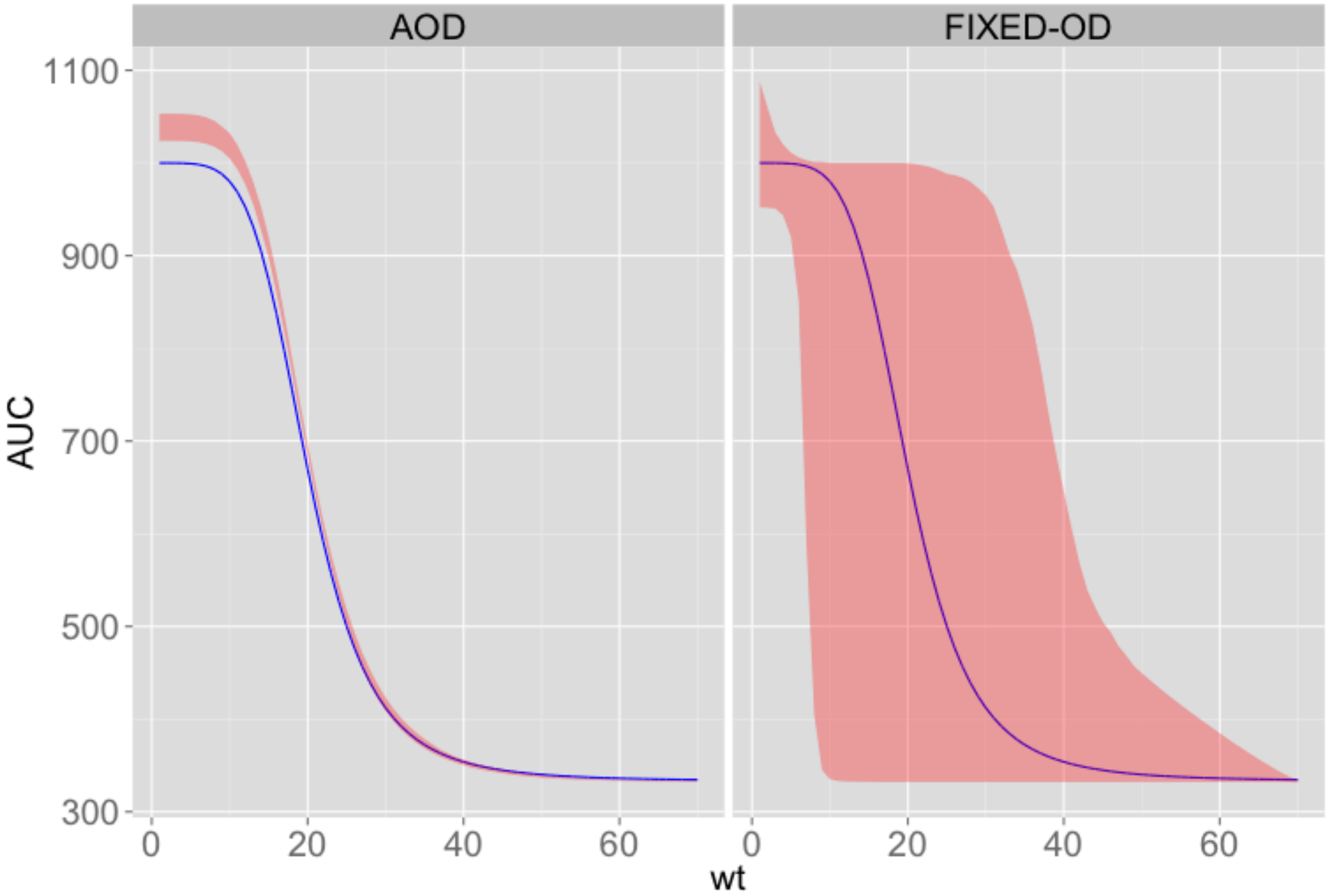
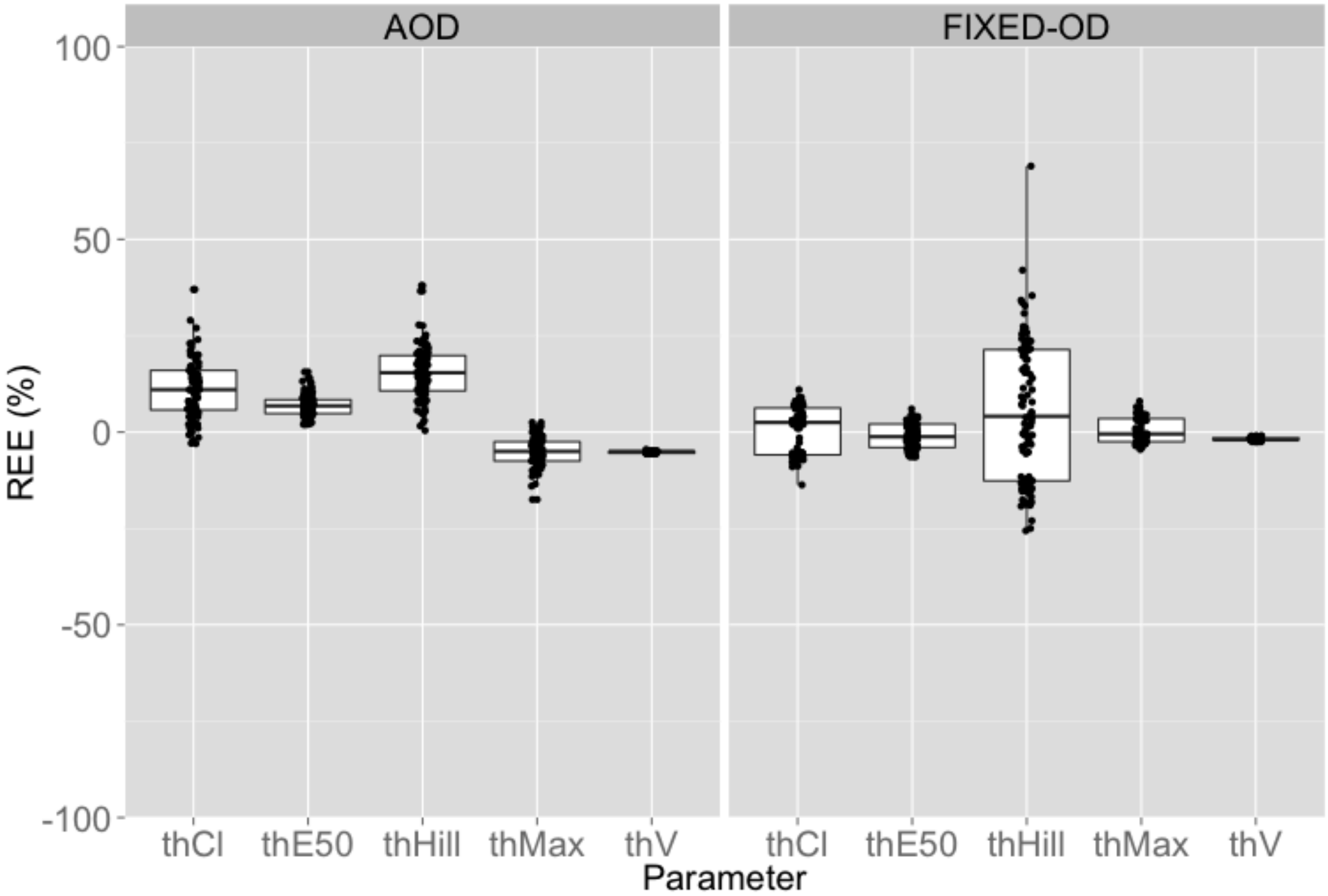


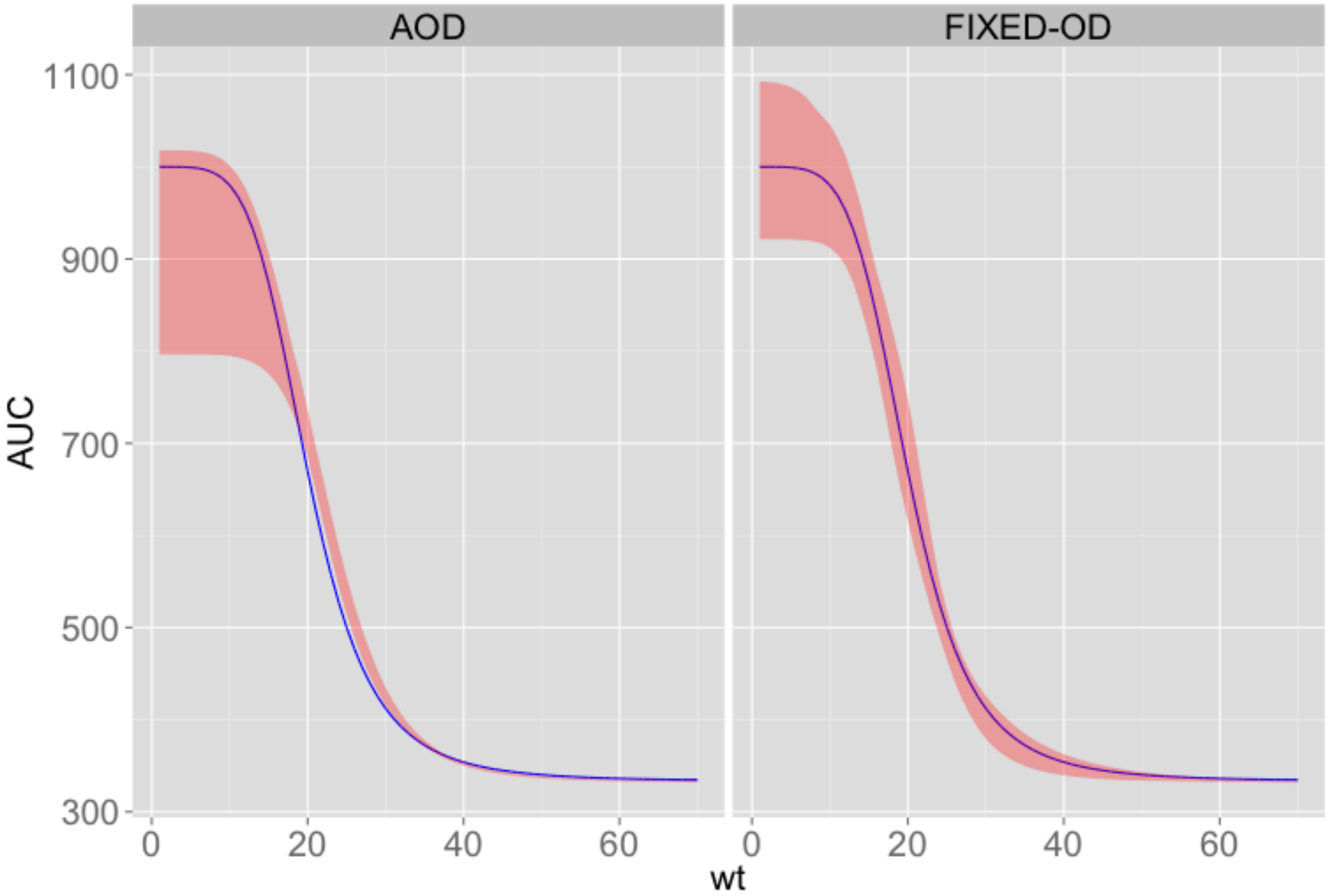
Prediction of AUC for a fixed dose



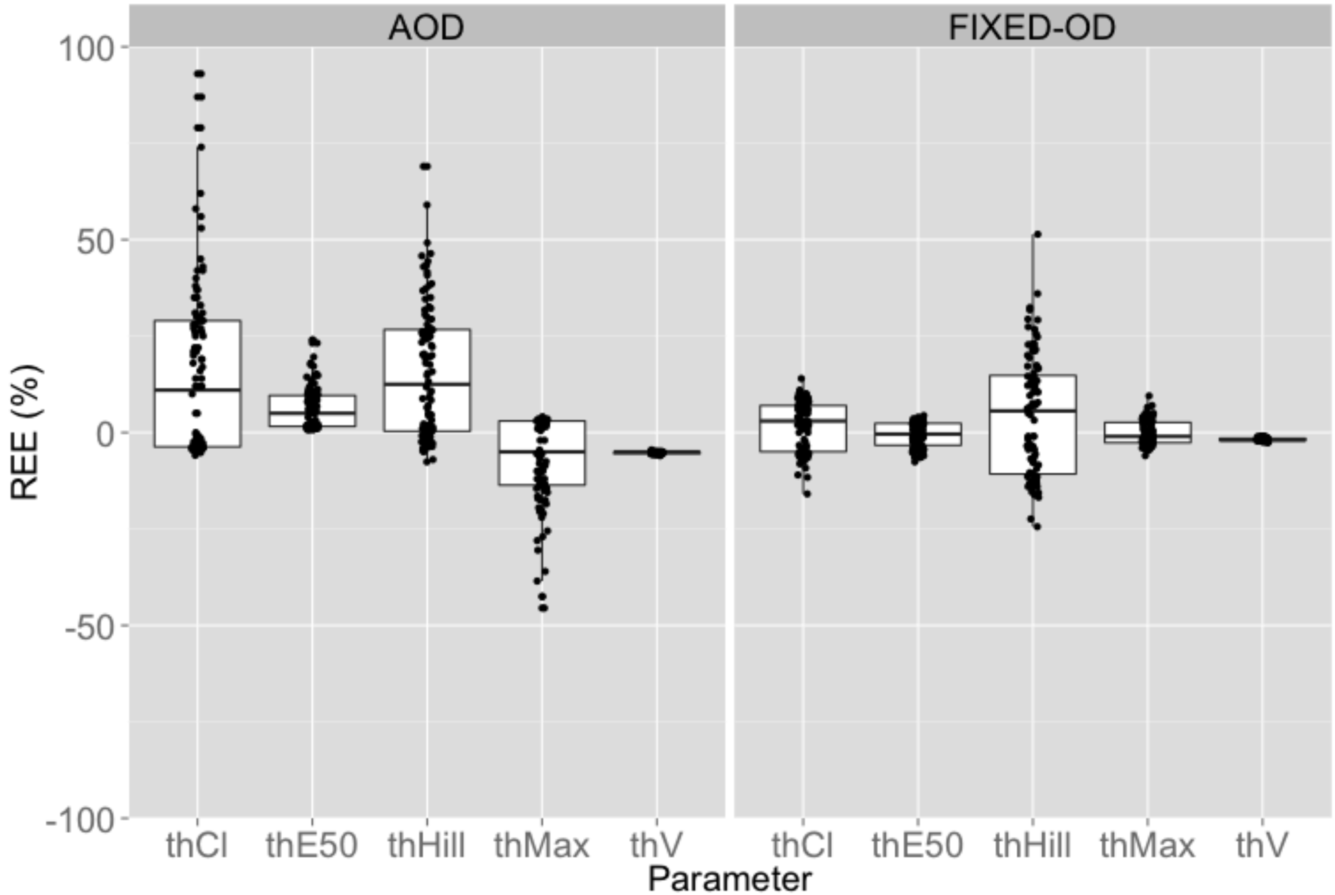
No Misspecification



No Misspecification

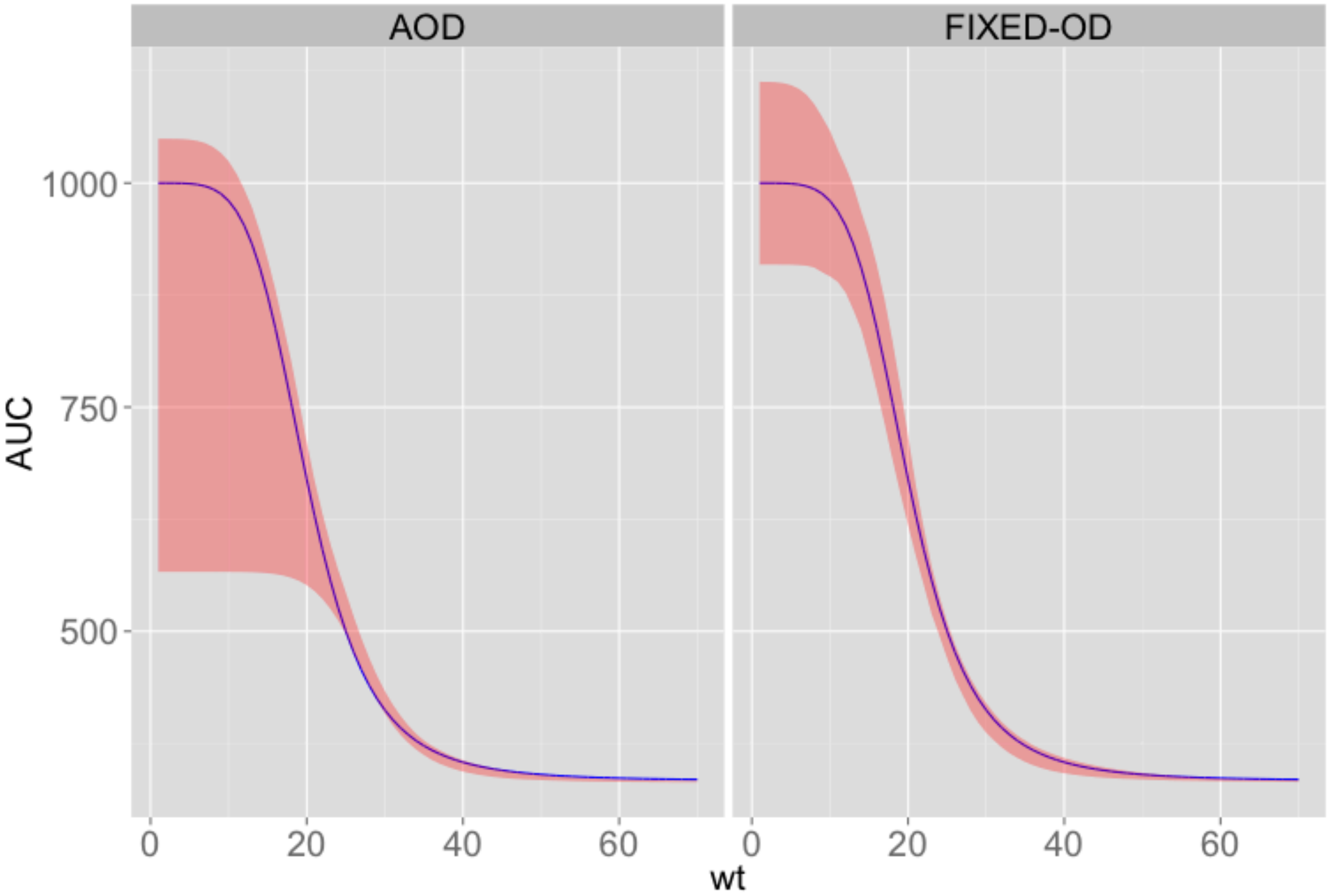


EMAX misspecification



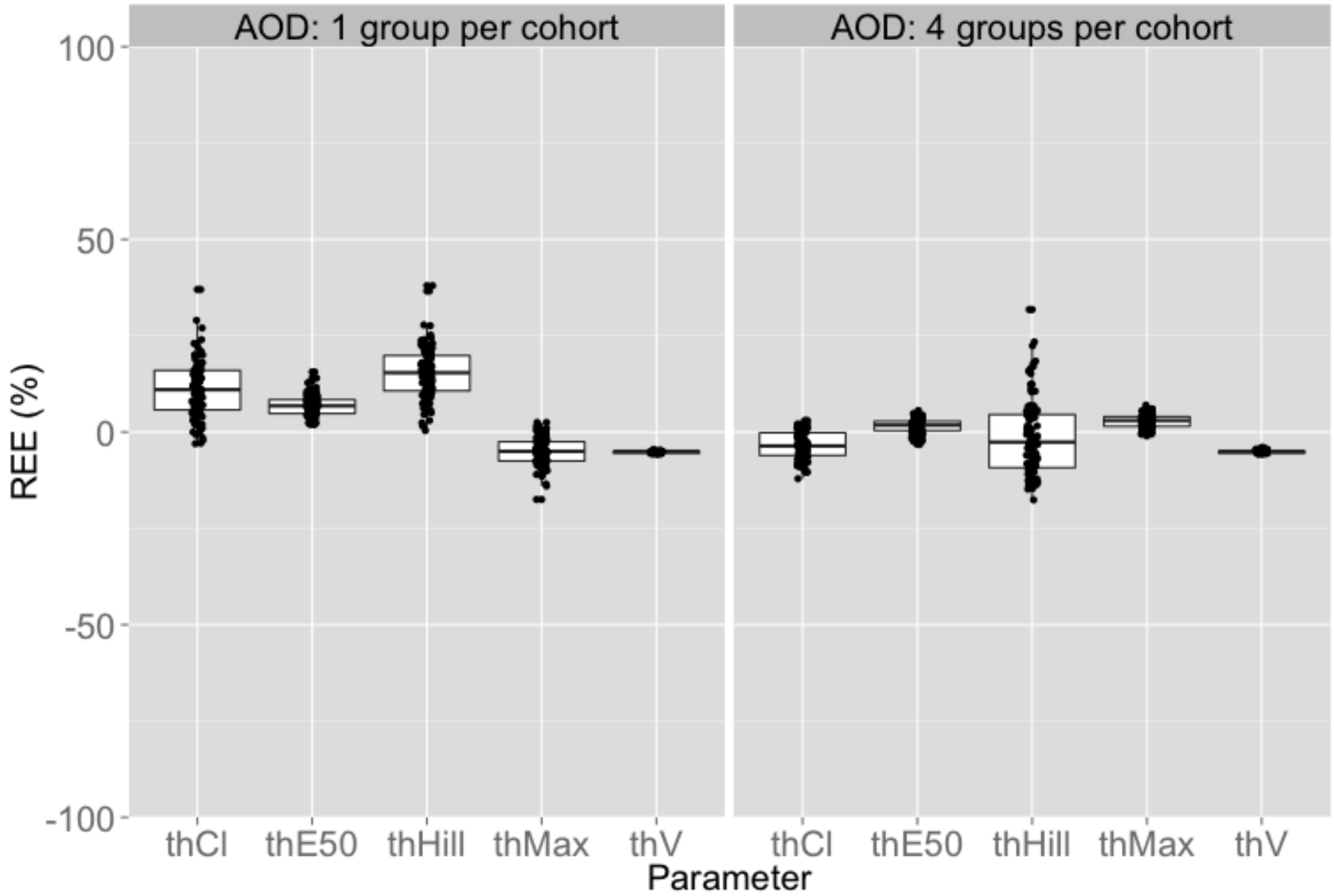
Prior: EMAX = 0.01
Truth: EMAX = 2

EMAX misspecification

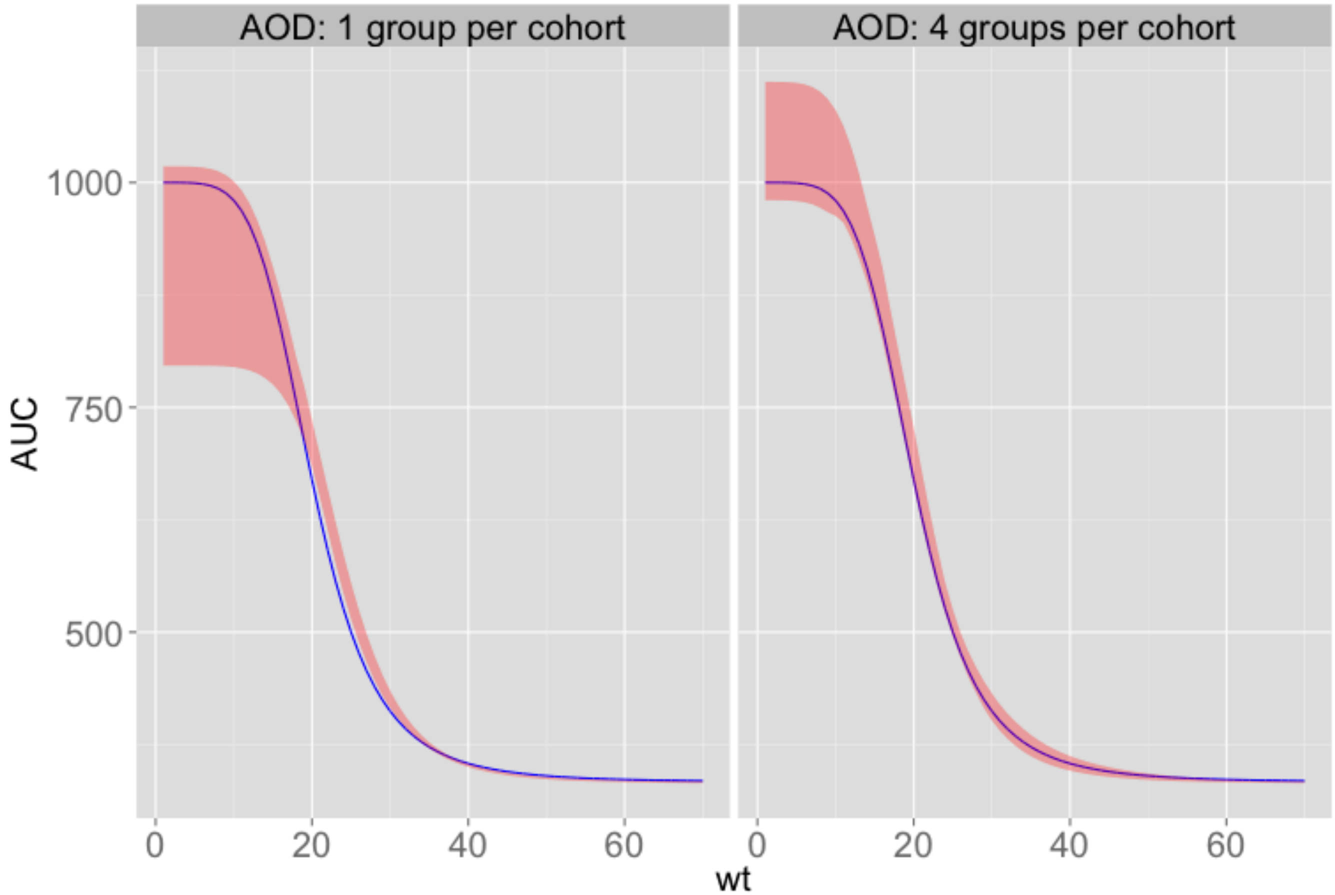


Prior: EMAX = 0.01
Truth: EMAX = 2

Comparing different AOD strategies.



Comparing different AOD strategies (2).



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Conclusions

- We successfully developed an initial implementation of a modular and flexible AOD computational platform, which will be available as freeware when released.
- In many cases AOD can improve parameter precision and accommodate for initial model misspecification compared to standard optimal design techniques.
- If no adaptation is needed or if the adaptation process is not carefully chosen a decrease in parameter precision or even parameter bias can be introduced, demonstrating the need for prior investigation, through simulation, of the AOD process.

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