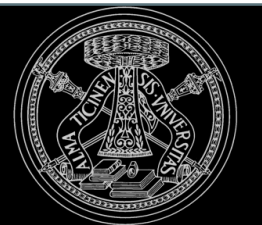
Paediatric trial design optimization using prior knowledge in combination with modelling & simulations

Elisa Borella, Sean Oosterholt, Paolo Magni, Oscar Della Pasqua

Lewis Sheiner Student Session

PAGE 2017



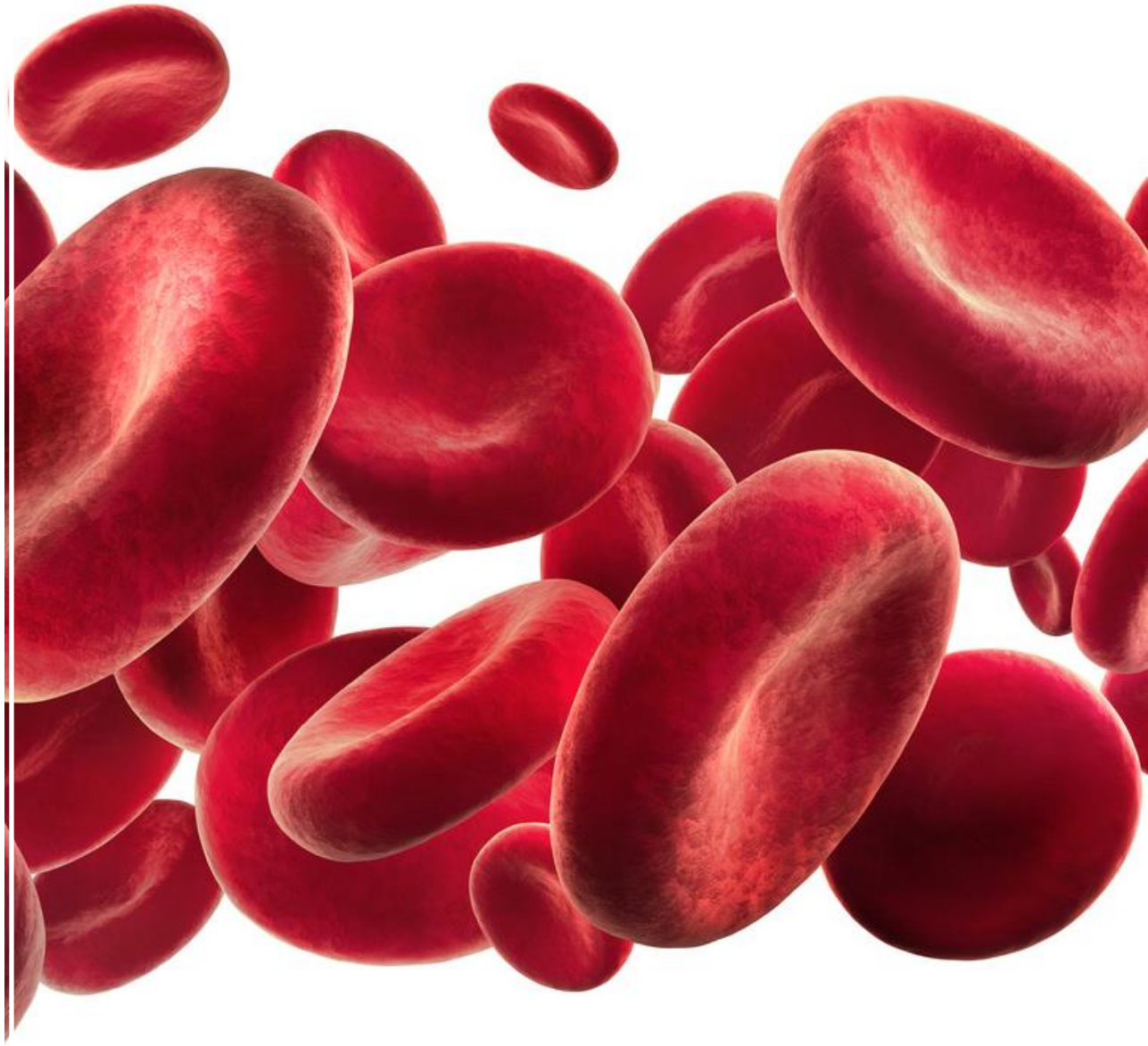
β-thalassemia

Rare hereditary blood disorder

- reduced Hb level in RBC
- reduced RBC production
- anemia

1/100,000 per year

Frequent RBC transfusions
→ **Iron overload**
→ Iron chelators



DEEP project

DEEP-2 study

DEFERIPRONE EVALUATION IN PAEDIATRICS

– Efficacy study

To **assess non-inferiority** of deferiprone (DFP) compared to deferasirox (DFX) in paediatric patients (1 month – 18 years)

- Primary endpoint: change in serum ferritin from baseline after 1 year

– PK sub-study **(at the end of the 1 year efficacy study)**

To **characterize DFX exposure** in paediatric patients (1 year - 18 years)

Knowledge gaps

DEEP-2 PK sub-study

To **characterize DFX exposure** in paediatric patients

A popPK model for DFX is needed

Issues

- ✓ very sparse PK data
- ✓ few subjects

Knowledge gaps

DEEP-2 PK sub-study

To **characterize DFX exposure** in paediatric patients

A popPK model for DFX is needed

Issues

- ✓ very sparse PK data
- ✓ few subjects

Objective n° 1

Evaluate to what extent the use of

prior knowledge (adult PK data)

+

allometry (and maturation)

can support **the analysis of very sparse PK data**

Knowledge gaps

DEEP-2 PK sub-study

To **characterize DFX exposure** in paediatric patients

A popPK model for DFX is needed

Issues

- ✓ very sparse PK data
- ✓ few subjects

Objective n° 2

Evaluate to what extent the use of

prior knowledge (adult PK data)

+

ED-optimization methods

can support **the design of future paediatric PK studies with chelating agents**

Knowledge gaps

DEEP-2 efficacy study

To **assess non-inferiority** of
DFP compared to DFX in 1 year

Issues

- ✓Time to response set to 1 year by empiricism
- ✓Some patients may be treated with suboptimal doses for a long period

Knowledge gaps

DEEP-2 efficacy study

To **assess non-inferiority** of DFP compared to DFX in 1 year

Issues

- ✓ Time to response set to 1 year by empiricism
- ✓ Some patients may be treated with suboptimal doses for a long period

Objective n° 3

Evaluate to what extent the use of

prior knowledge
(adult/pediatric efficacy data)

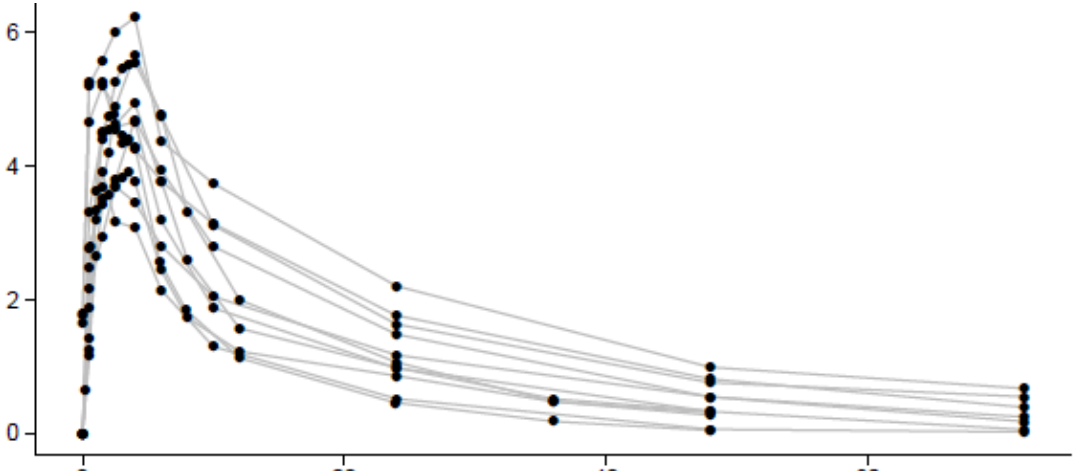
+

drug-disease models

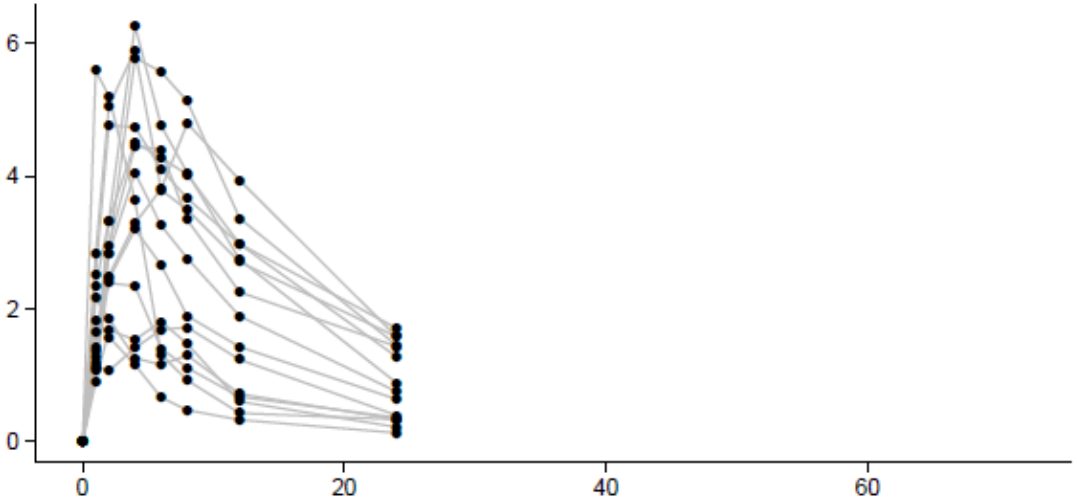
allows **prediction of clinical response** earlier than 12 months as well as **optimization of drug therapy**

Population DFX PK model

Mean data from several PK studies

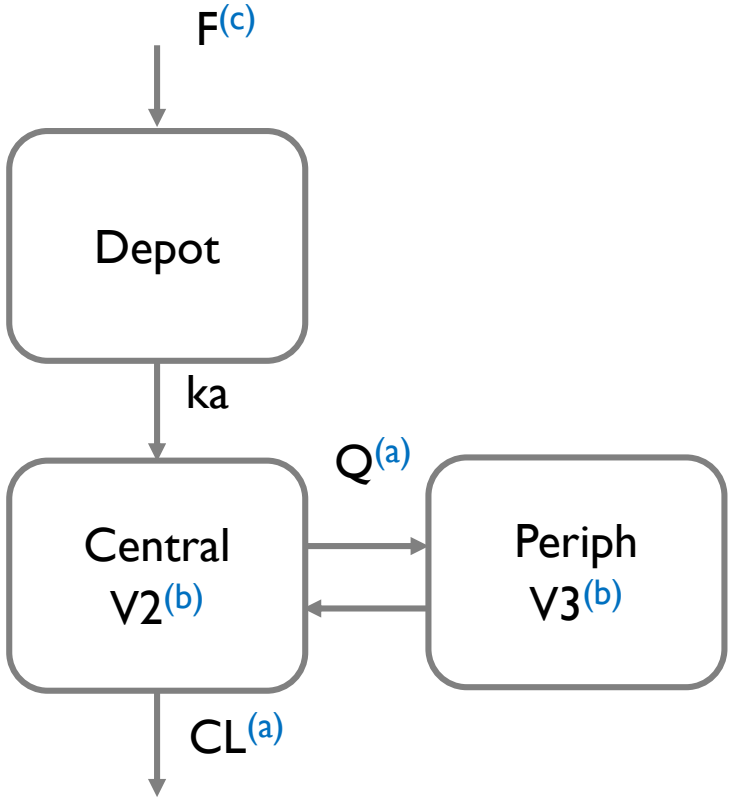


Individual data from a single PK study



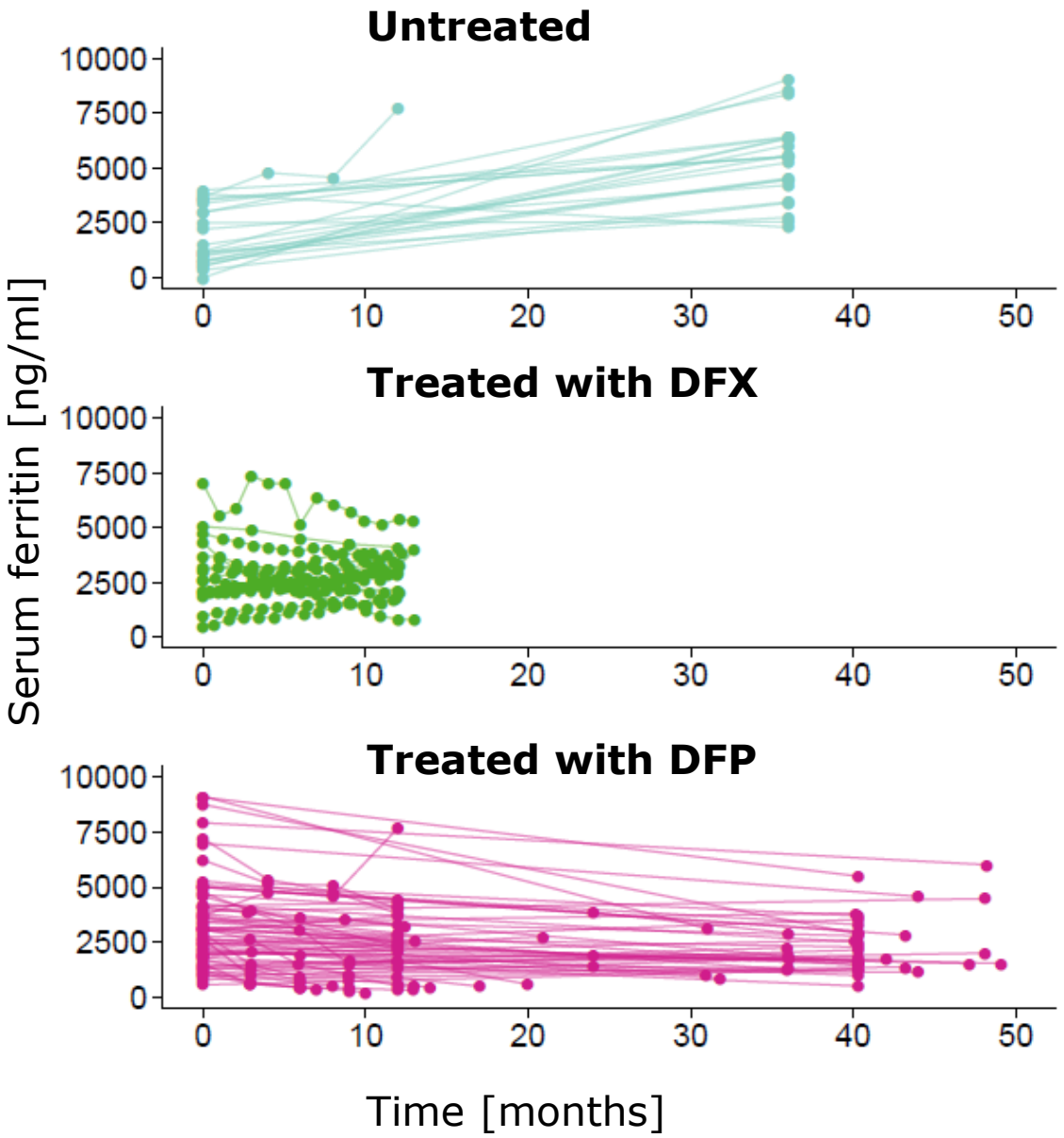
DFX concentration normalized by dose [µM/mg/kg]

Time after dose [hours]



(a) $PAR = POP\_PAR \cdot (WEIGHT/70)^{0.75}$
(b) $PAR = POP\_PAR \cdot (WEIGHT/70)^{1}$
(c) Fixed to the value reported in Sechaud *et al.* J Clin Pharmacol, 48(8), 2008

Population drug-disease model for iron overload



Transfusional iron input
(mg iron/kg/month)
[=1.6 · BLOODCONS (ml RBC/kg/month)]

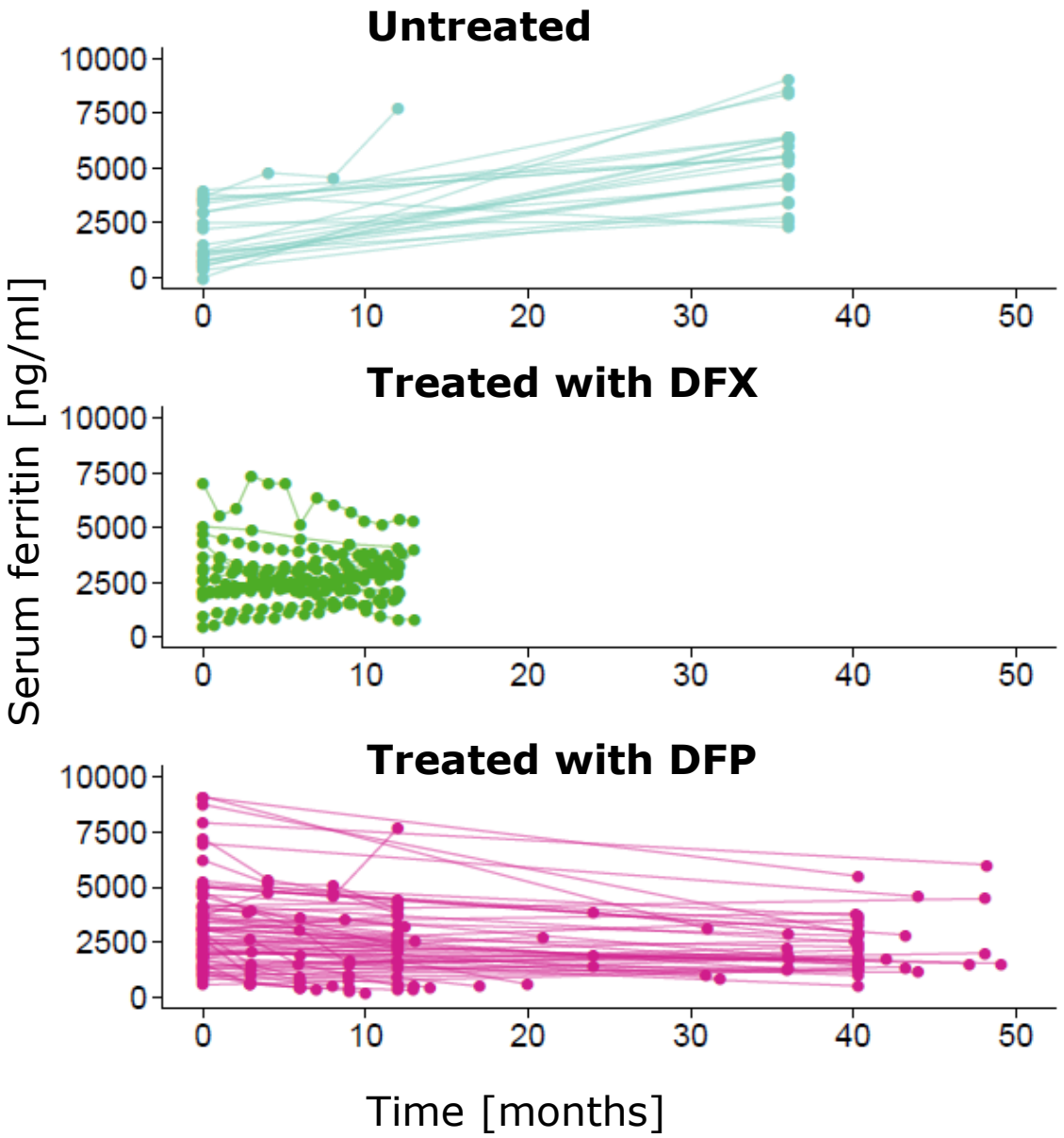
$$\frac{\text{FerMax} \cdot \text{Iron}}{\text{Fer50+Iron}}$$

Iron → Ferritin (in plasma)

Iron (t=0)= $\frac{\text{Fer50} \cdot \text{BASELINE}}{\text{FerMax} - \text{BASELINE}}$

$D_{eff} = \text{Slope} \cdot C_{ss}^{av}$

Population drug-disease model for iron overload



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Iron

Ferritin
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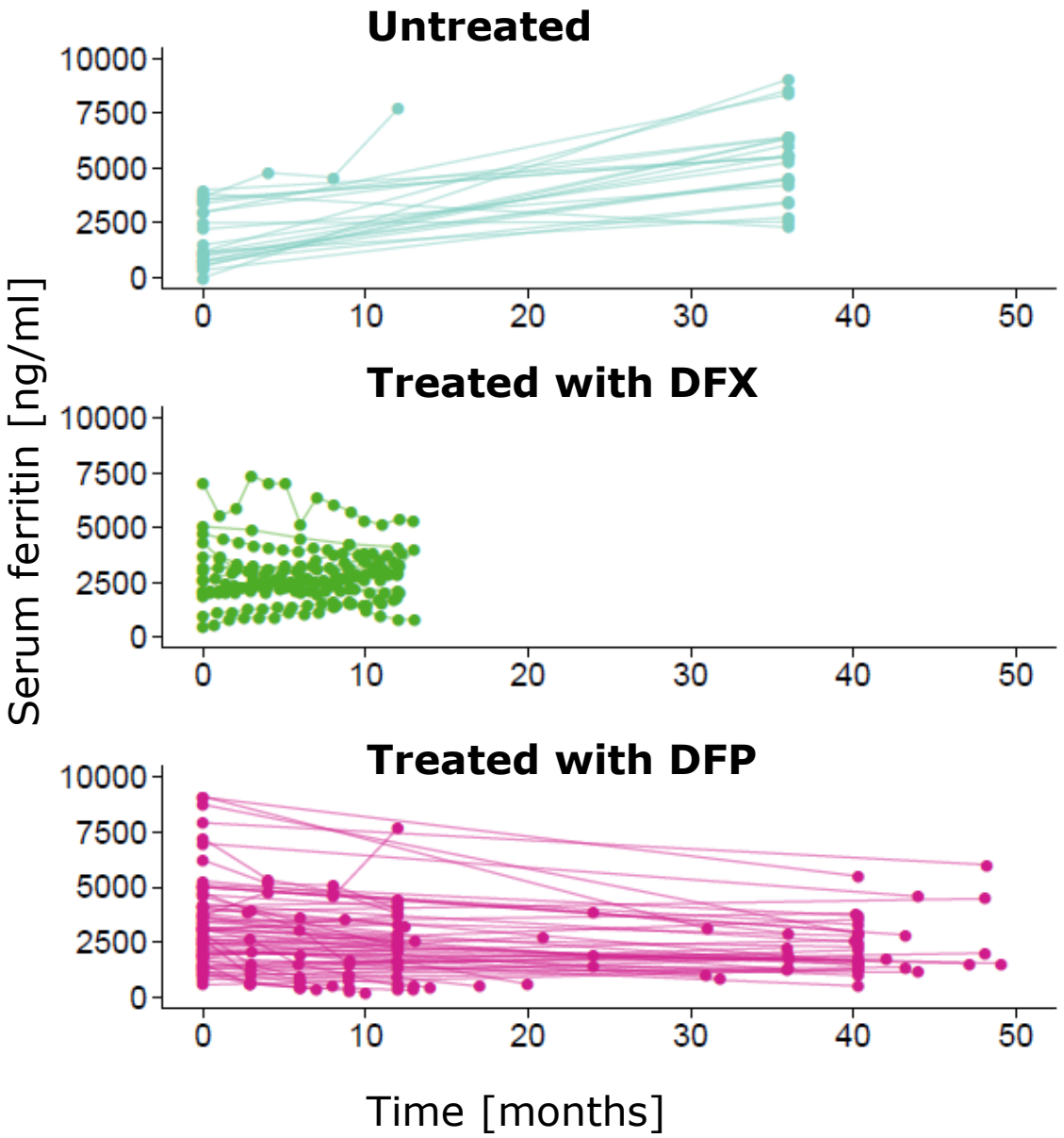

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$D_{eff} = \text{Slope} \cdot C_{ss}^{av}$

Objective n°1

Understanding the impact of prior knowledge on sparse PK sampling

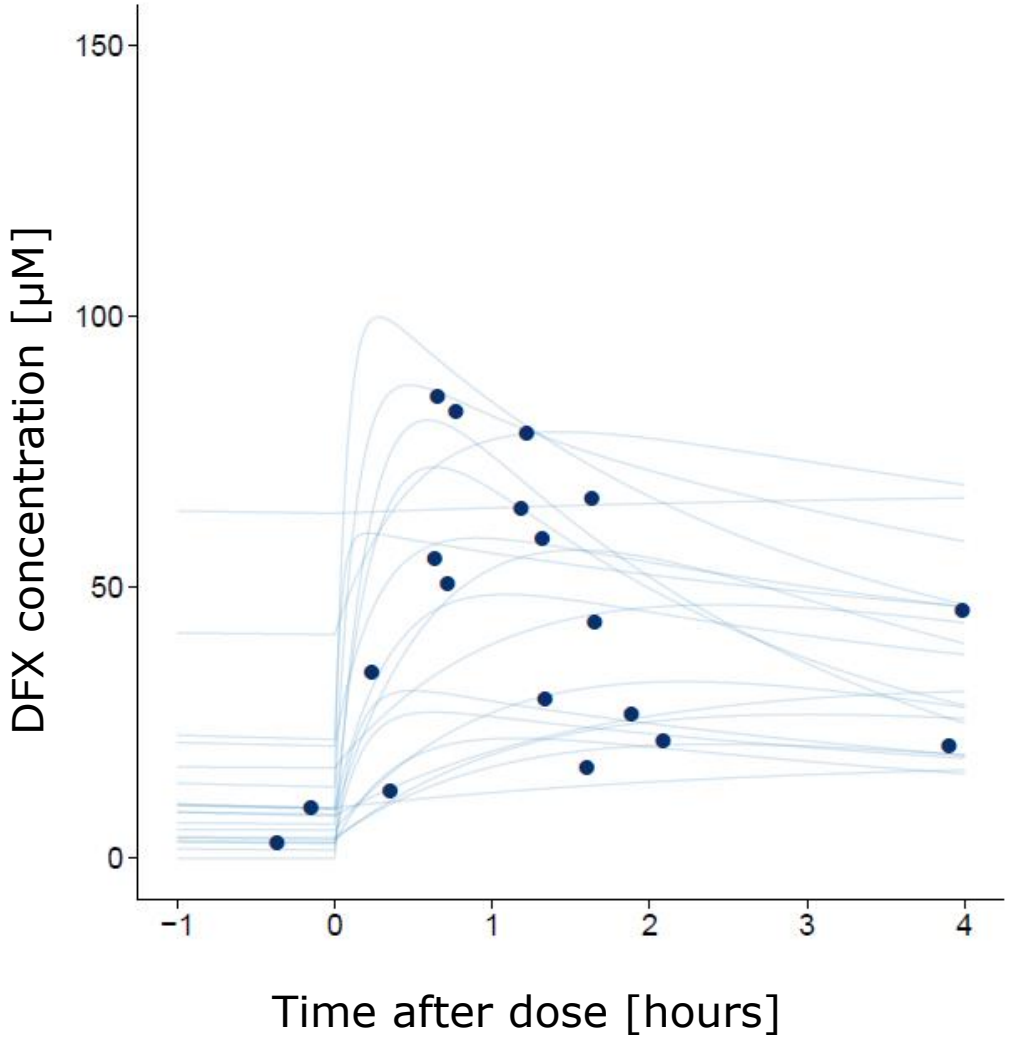
DEEP-2 PK sub-study

Protocol and sampling schedule

- 19 subjects
  - 1 year - 18 years
  - Affected by heamoglobinopathies

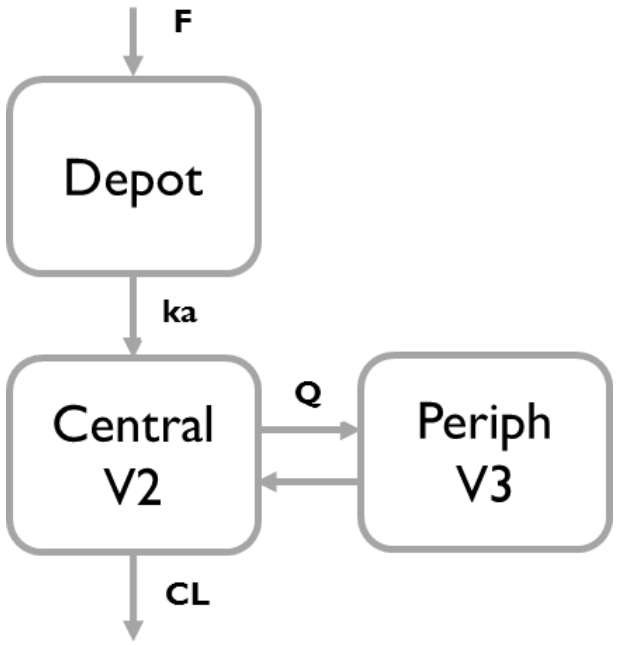
- 1 PK blood sample for each patient

Sampling times (minutes)									
PreDose	T1	T2	T3	T4	T5	T6	T7	T8	T9
-15	15	30	45	60	75	90	105	120	240



I. Simulation of paediatric PK profiles

from 1 h pre-dose to 4 hrs post-dose



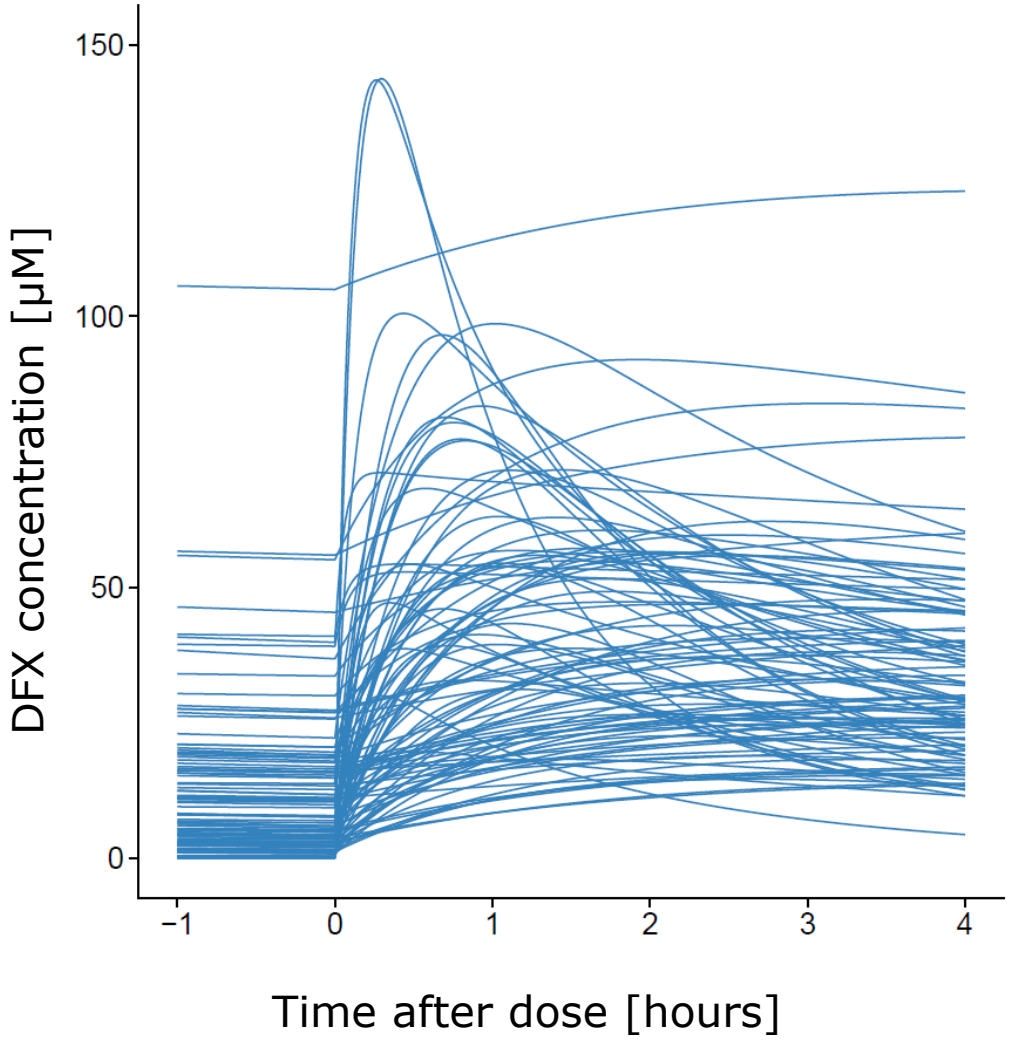
+ DFX dose 20 mg/kg (at SS)

+ DEEP-2 study patients covariates

- Weight=f(PMA,Sex)[2]

  PMA: 1 – 18 years
  1:1 sex ratio

[2]Sumpter *et al.* Paediatr Anaesth, 21(3), 2011



I. Simulation of paediatric PK profiles

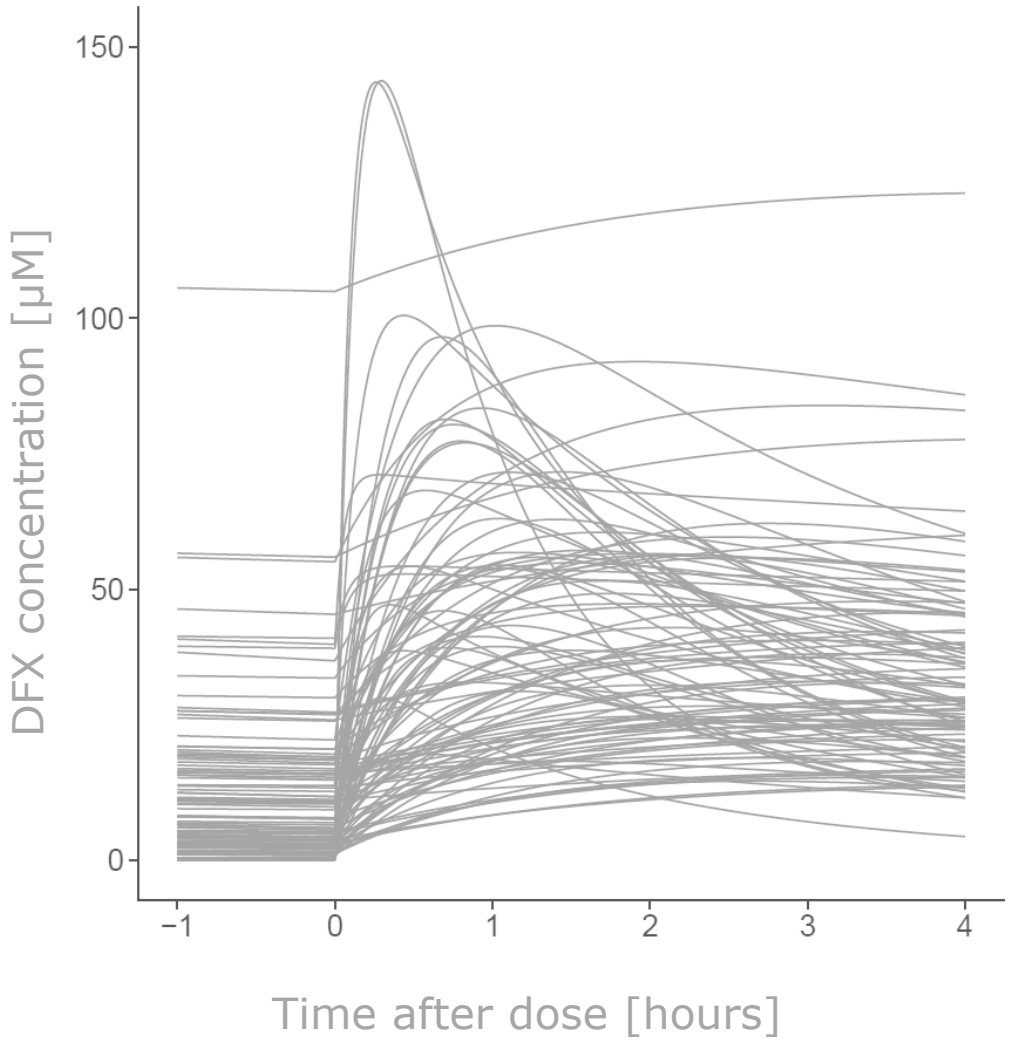
from 1 hr pre-dose to 4 hrs post-dose

Scenario 1

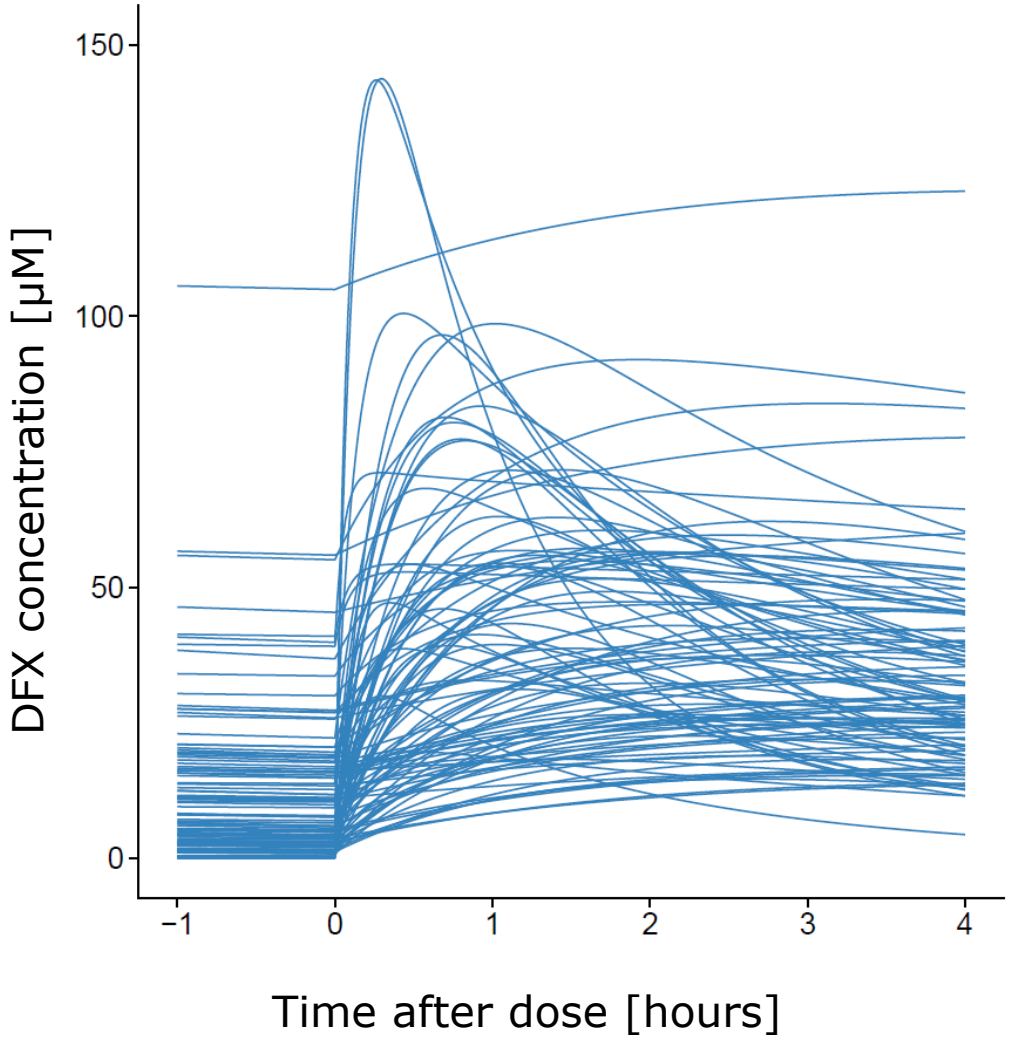
- Parameters allometrically scaled

Scenario 2 (with sub-scenarios)

- Different model parameters *or*
- Different allometric exponent



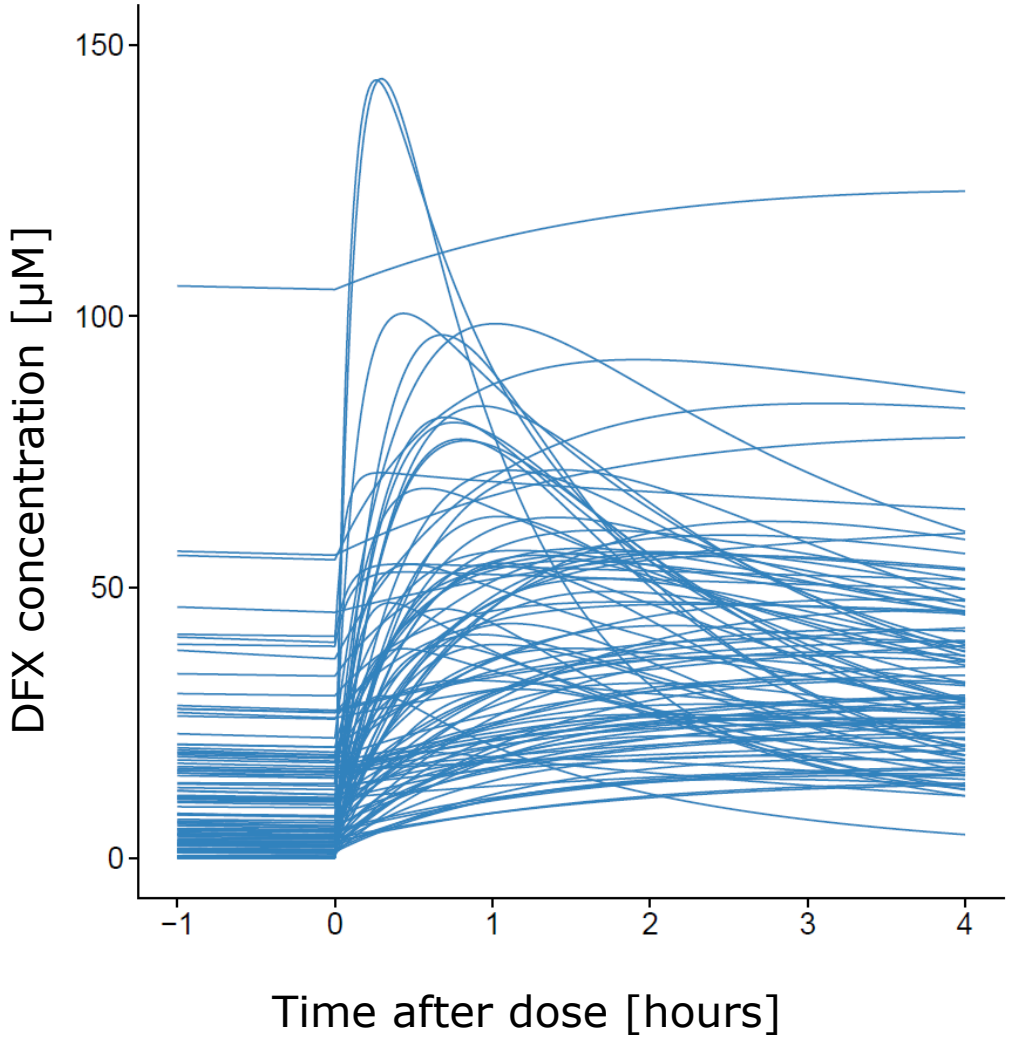
2. **Simulation-estimation of PK sub-study** with original protocol



2. **Simulation-estimation of PK sub-study** with original protocol

Extract

- 19 subjects
- 1 sample/subj



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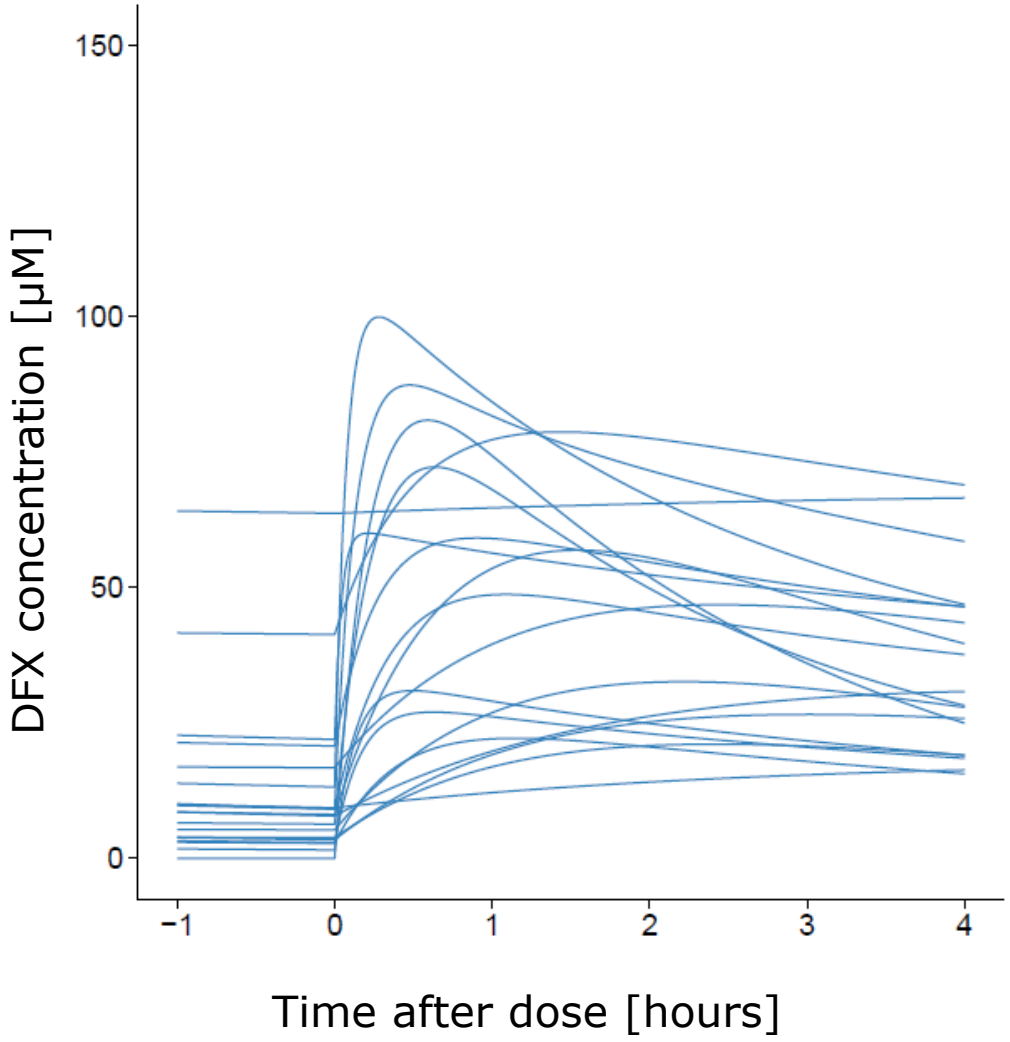

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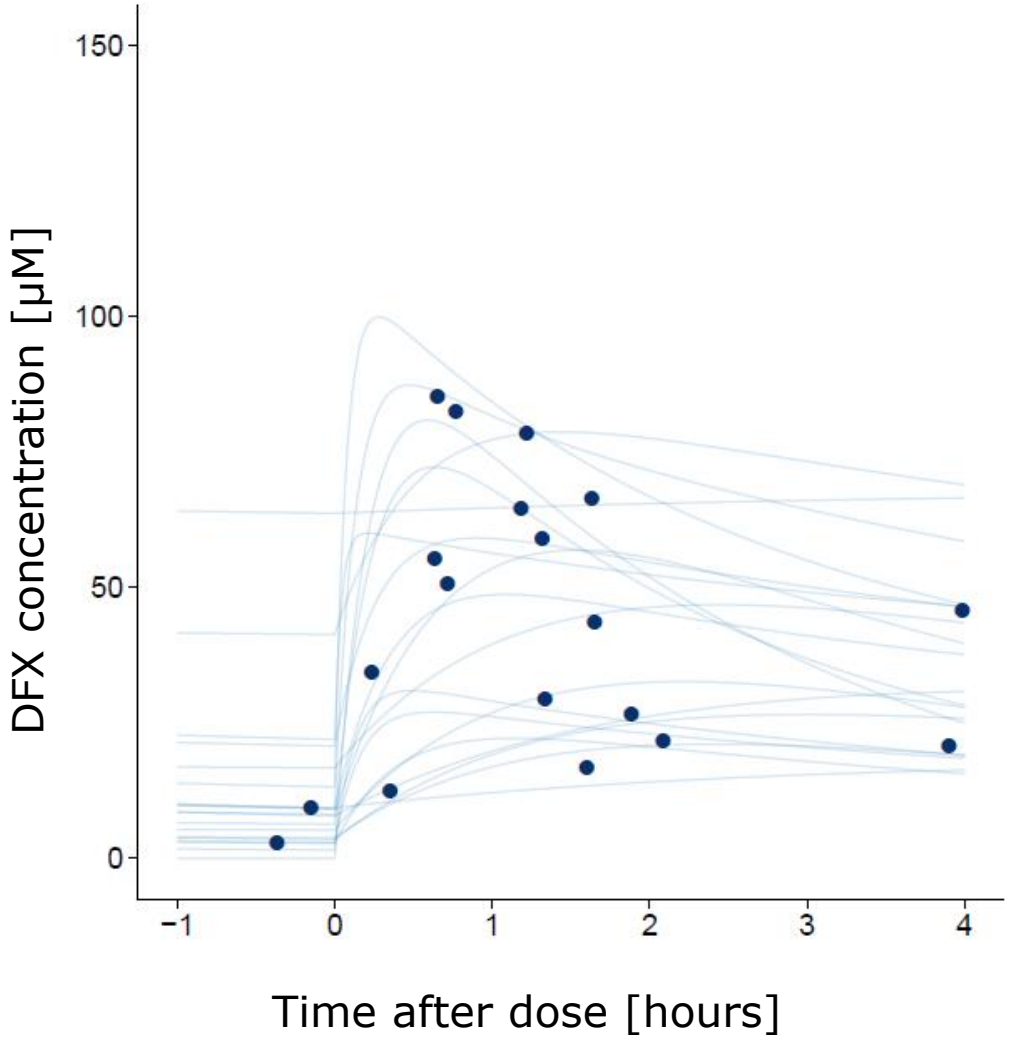


2. **Simulation-estimation of PK sub-study** with original protocol

Extract

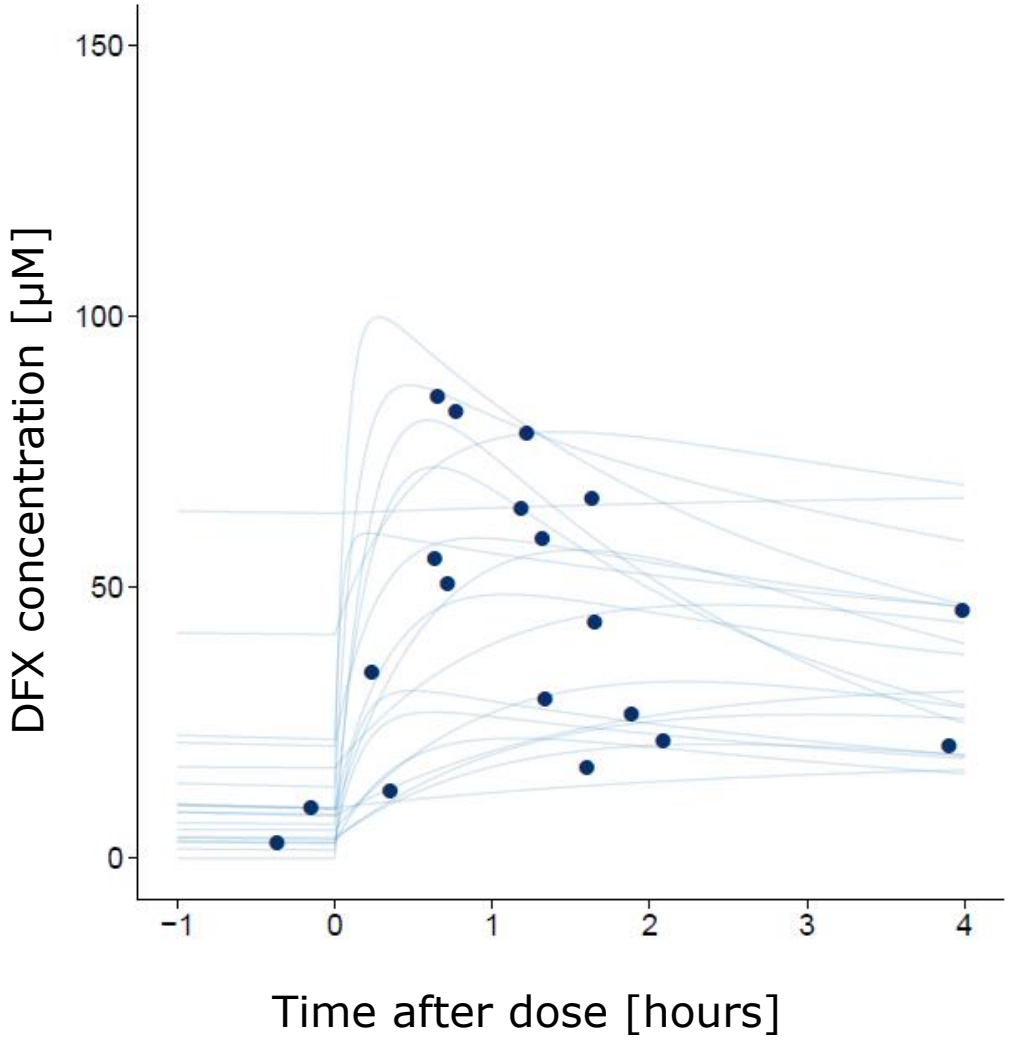
- 19 subjects
- 1 sample/subj

Estimate popPK model

- Typical values of CL, V2, V3, Q and ka
- IIV of CL, V2, V3 and ka

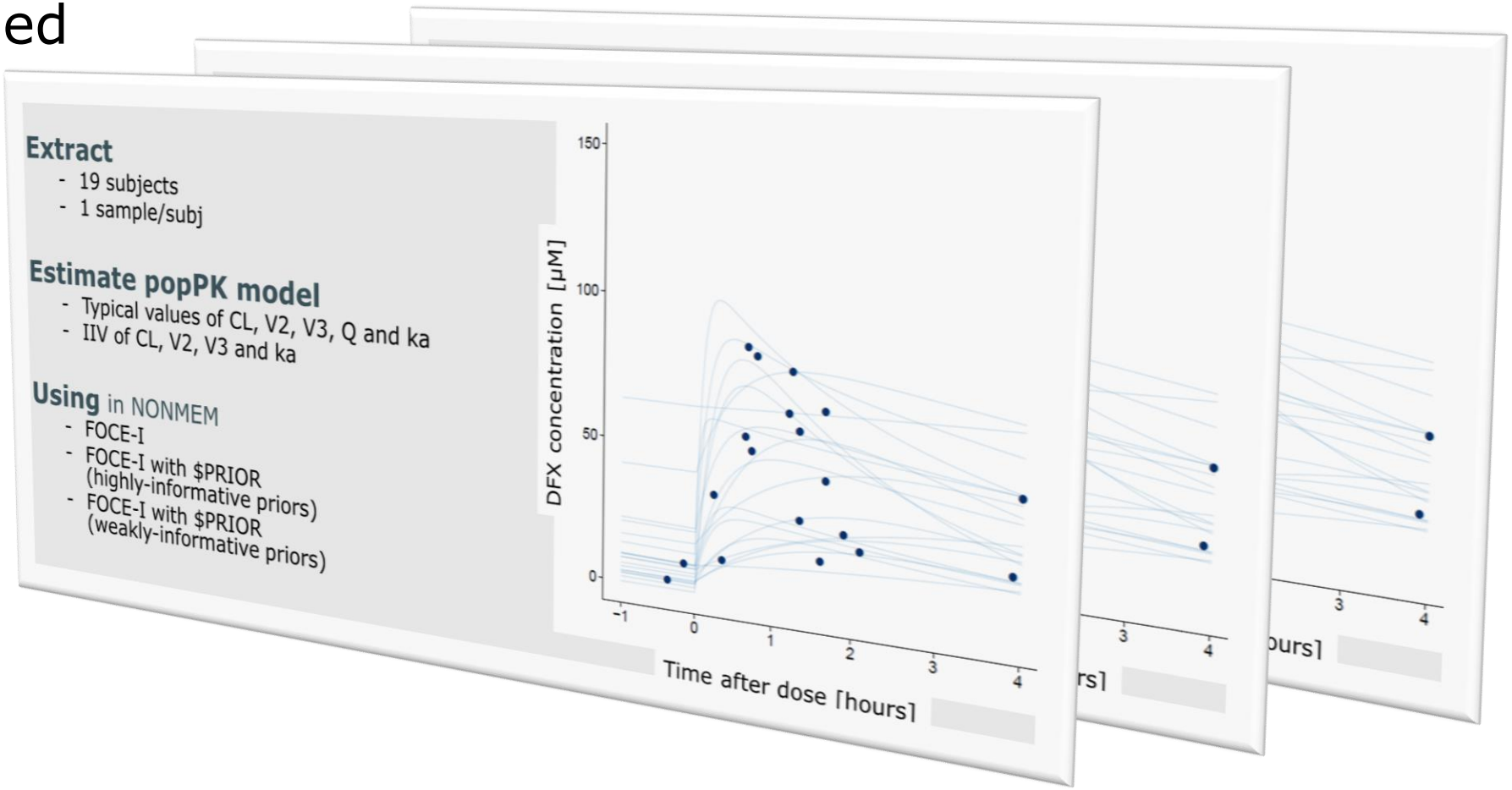
Using in NONMEM

- FOCE-I
- FOCE-I with $PRIOR (highly-informative priors)
- FOCE-I with $PRIOR (weakly-informative priors)



2. **Simulation-estimation of PK sub-study** with original protocol

Repeat until 100 successful runs are obtained



Results

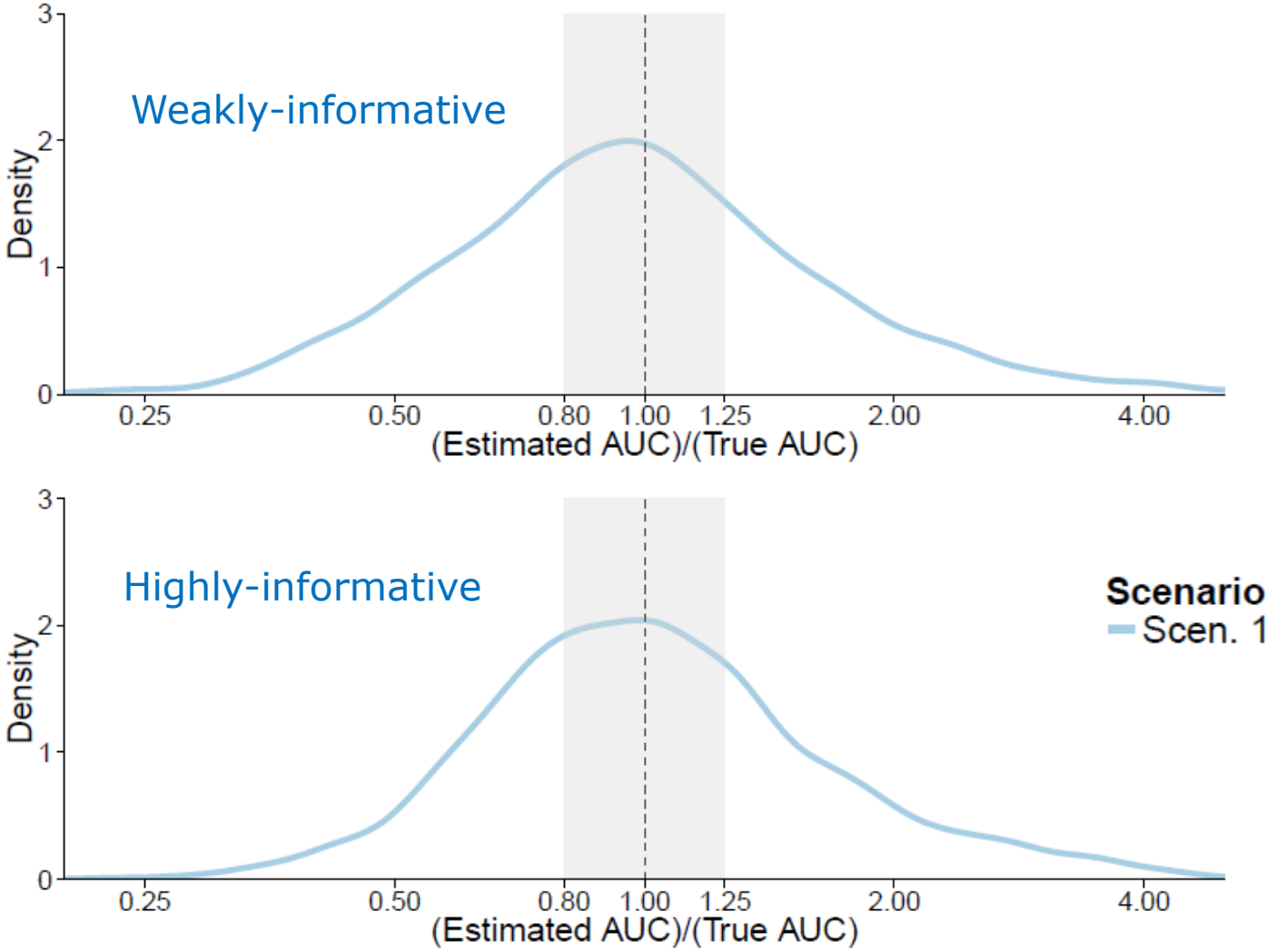
Comparison: No priors *vs* Priors

Type of sampling	N° of samples/subj	Scenario	Priors	Probability of successful run (%)
Protocol sampling	1	Scenario 1: only allometric scaling	Weakly-informative	56.50
			Highly-Informative	75.19
			No priors	12.22

$$\text{Probablity of succesful run (\%)} = \frac{100}{\text{n° of runs necessary to obtain 100 successful runs}} \cdot 100$$

Results

Comparison: Weakly-informative *vs* Highly-informative priors

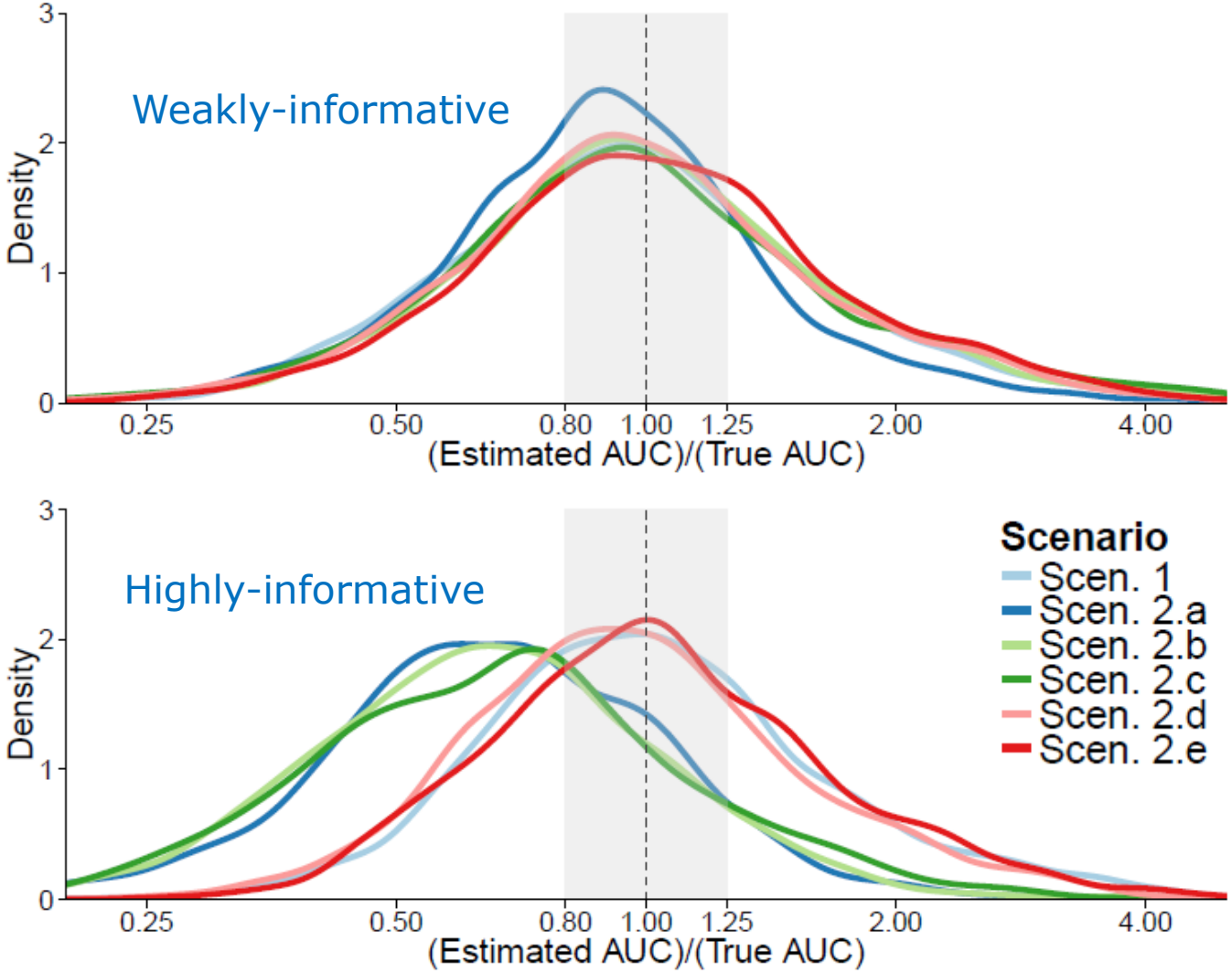


Scenario 1

- Parameters allometrically scaled

Results

Comparison: Weakly-informative *vs* Highly-informative priors



Scenario 1

- Parameters allometrically scaled

Scenario 2

a) $CL=CL_{adult}/2$

b) $CL=CL_{adult}/2$, $V2=V2_{adult}/2$

c) $CL=CL_{adult}/2$, $V2=V2_{adult}/2$, $Q=Q_{adult}/2$, $V3=V3_{adult}/2$

d) All. exp. CL/Q = 0.85

e) All. exp. CL/Q = 2/3

Objective n°2

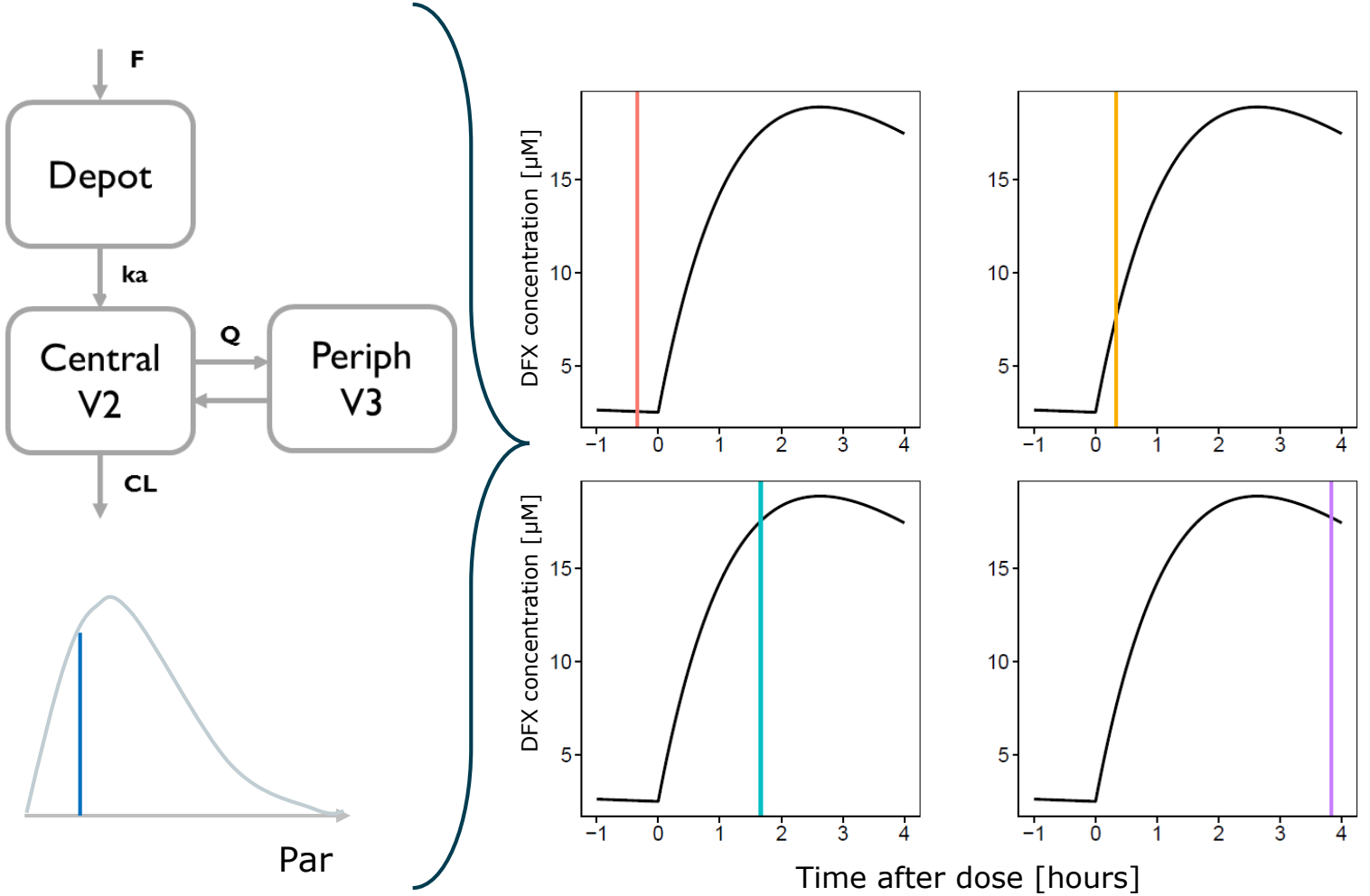
Optimization of sparse PK sampling times

I. Optimization of PK sampling schedule in PopED

ED-optimization

Uncertainties on model parameters

- Line Search method
- 19 subjects (according to current practice)
- 1 sample/subj between 1 h pre-dose to 4 hrs post-dose
- 4 designs



I. Optimization of PK sampling schedule in PopED

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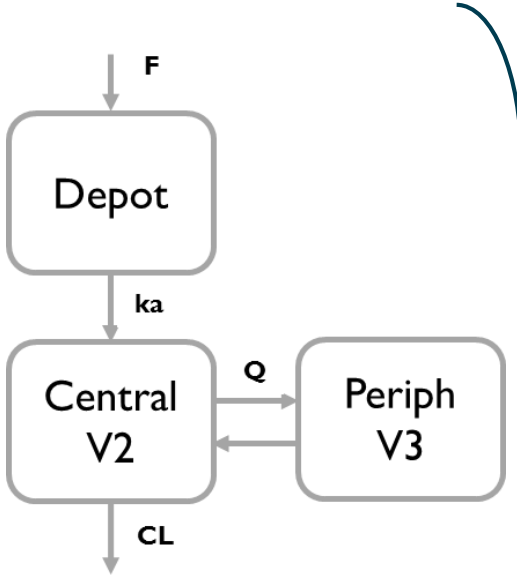

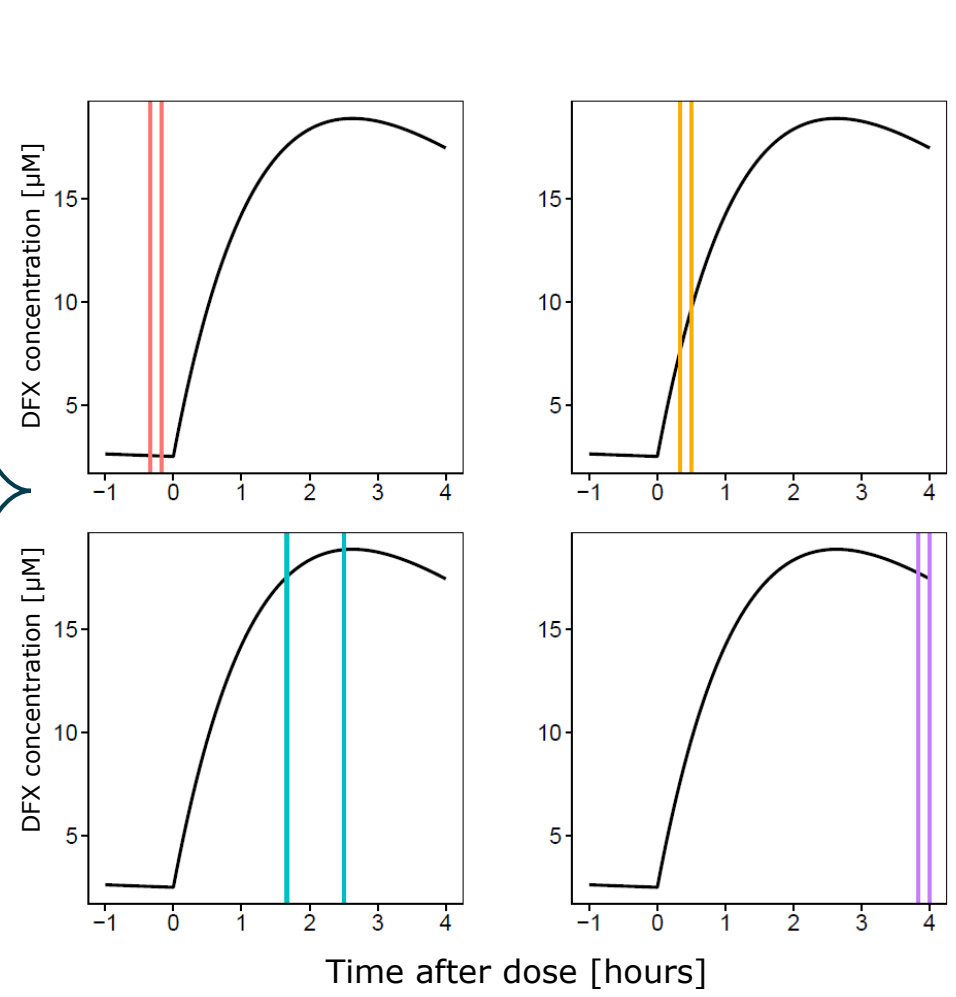

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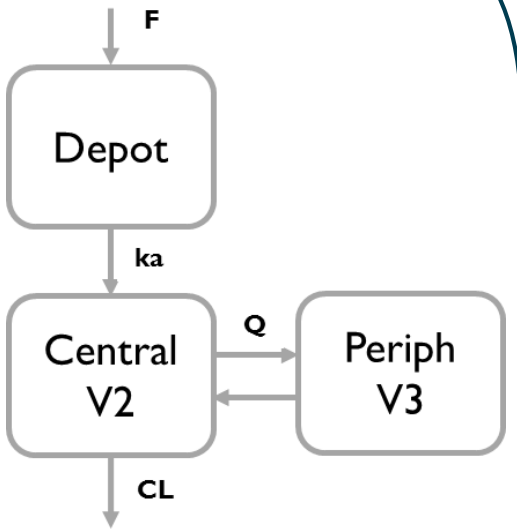
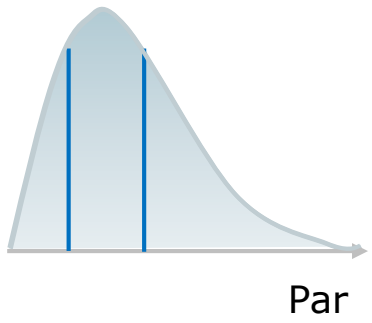
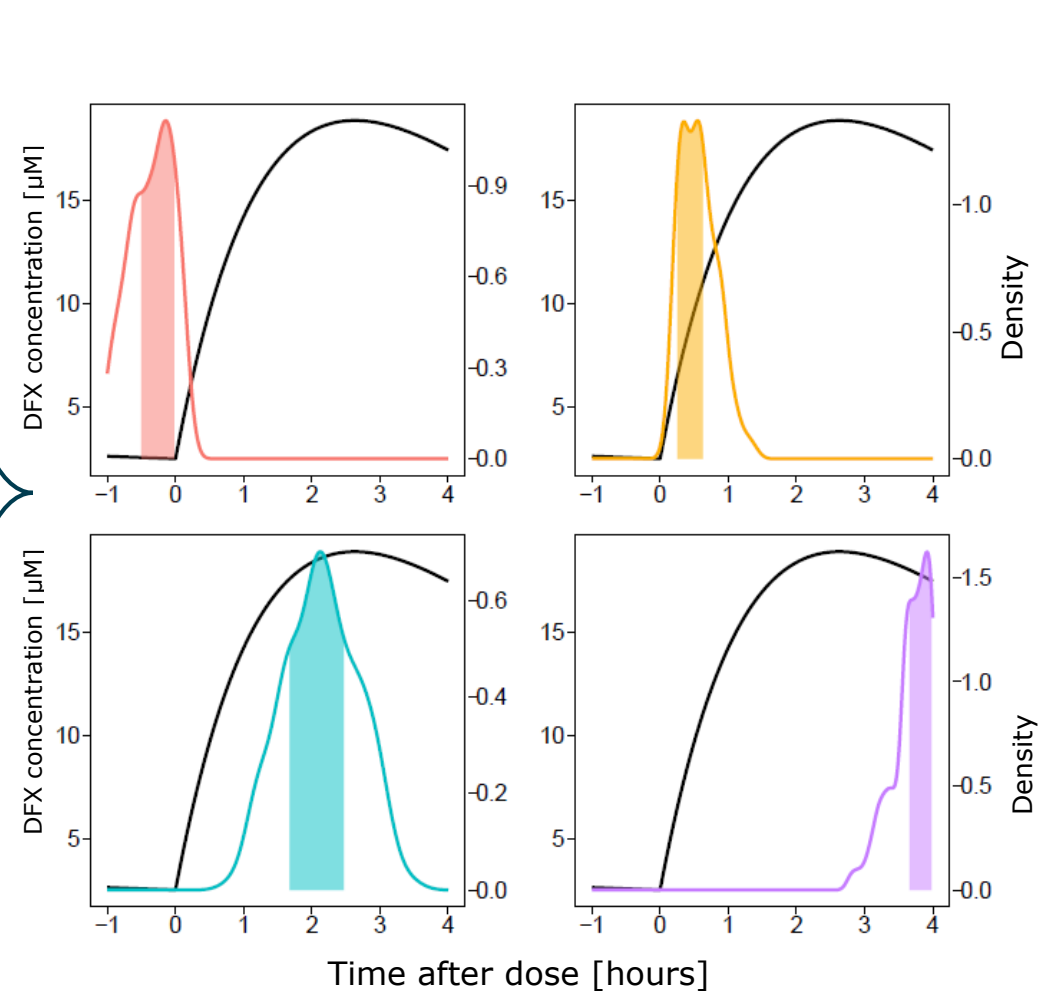
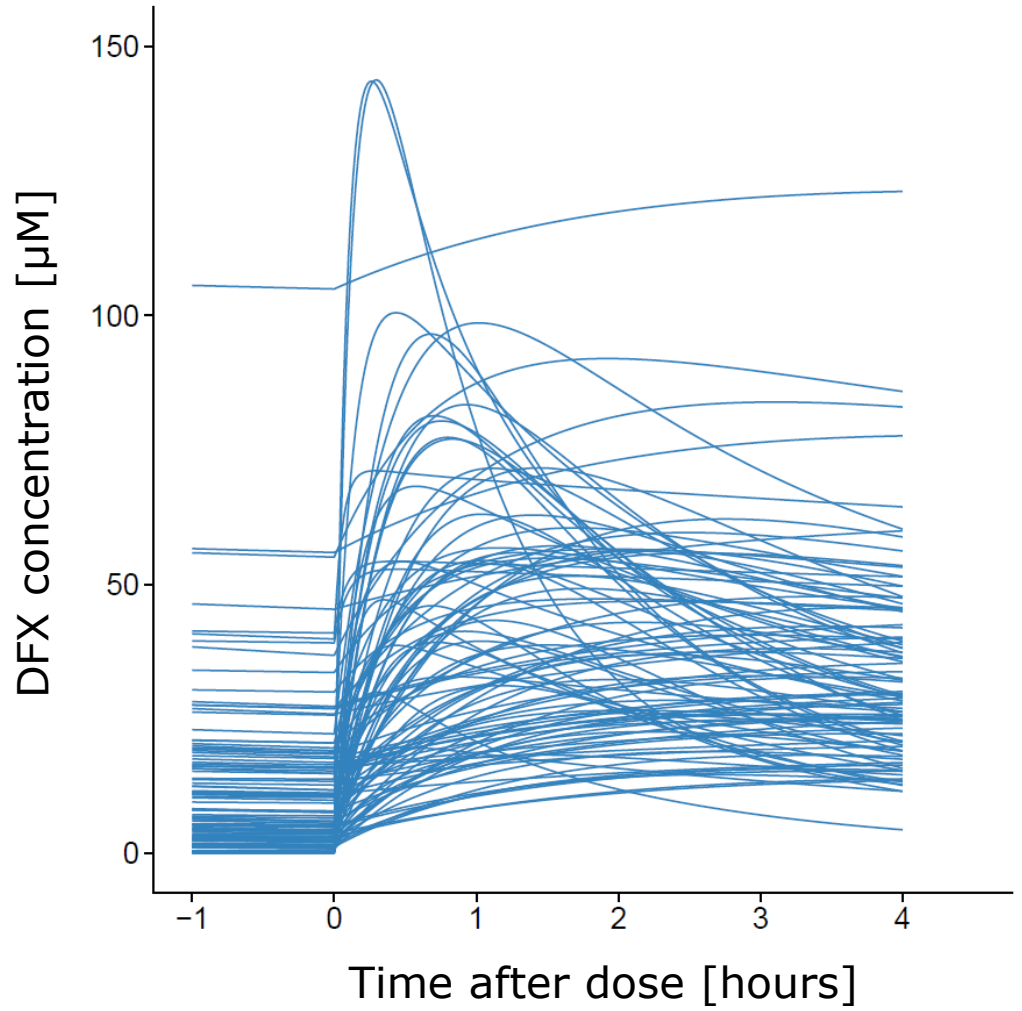






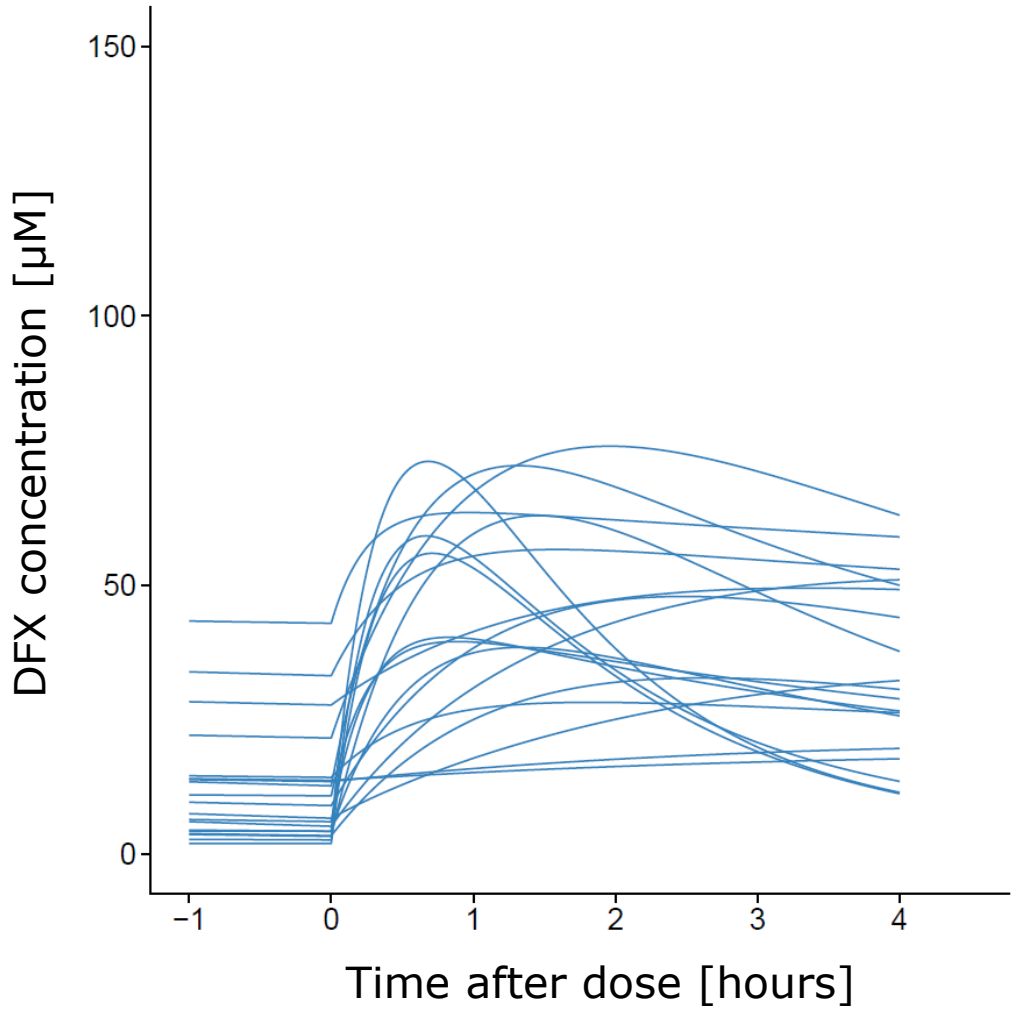
2. Simulation-estimation of PK sub-study with an optimized sampling scheme



2. **Simulation-estimation of PK sub-study** with an optimized sampling scheme

Extract

- 19 subjects
- **1 optimized sample per subject**



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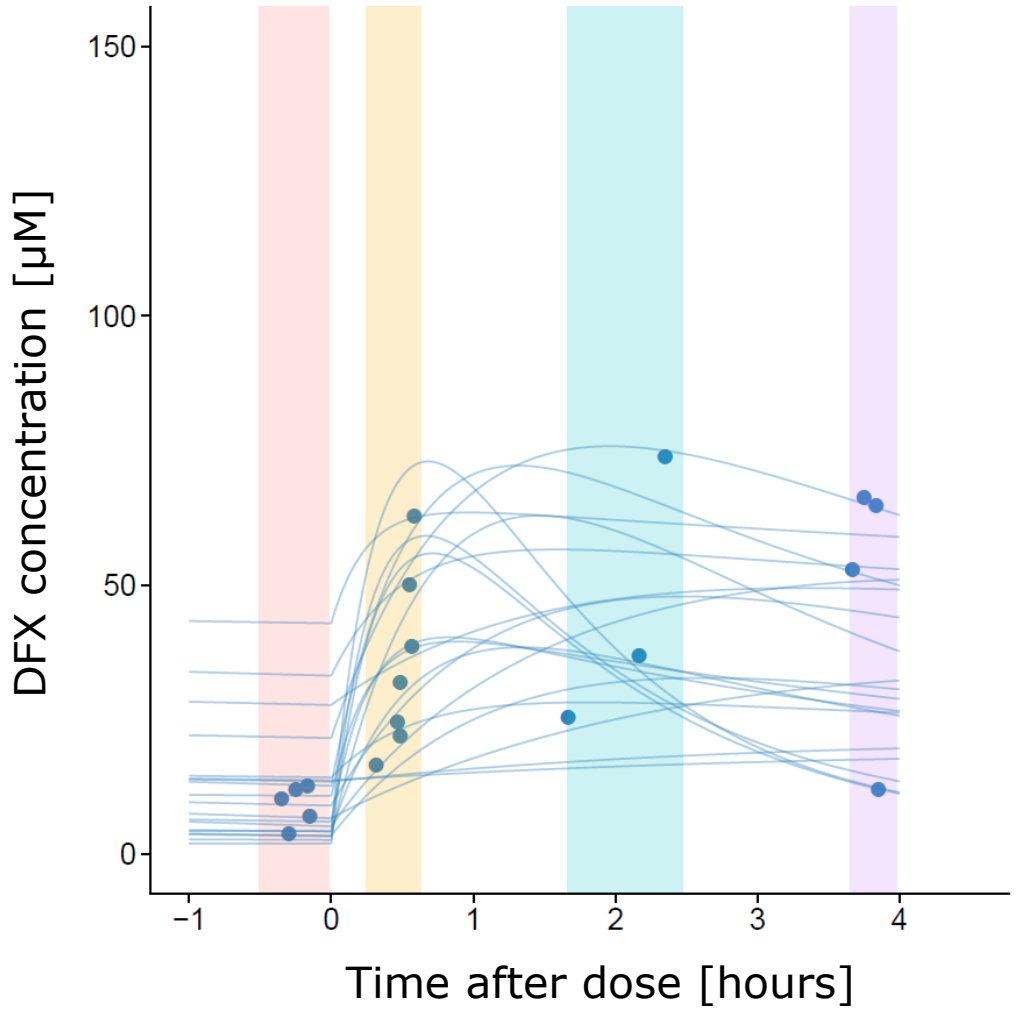

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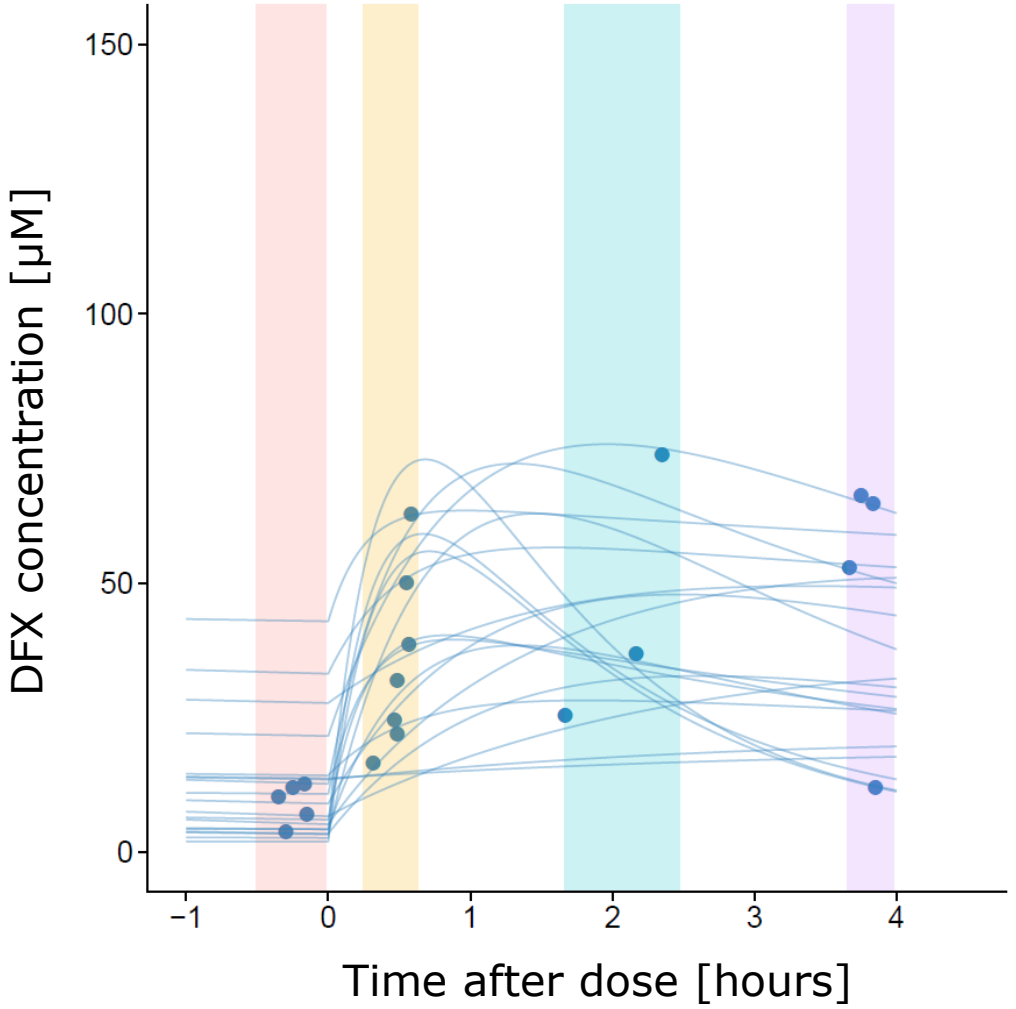
Estimate popPK model

- Typical values of CL, V2, V3, Q and ka
- IIV of CL, V2, V3 and ka

Using in NONMEM

- FOCE-I with $PRIOR (weakly-informative priors)

Only Scenario 1 (parameters allometrically scaled)



2. **Simulation-estimation of PK sub-study** with an optimized sampling scheme

Extract

- 19 subjects
- **2/3/4 optimized samples per subject**

Estimate popPK model

- Typical values of CL, V2, V3, Q and ka
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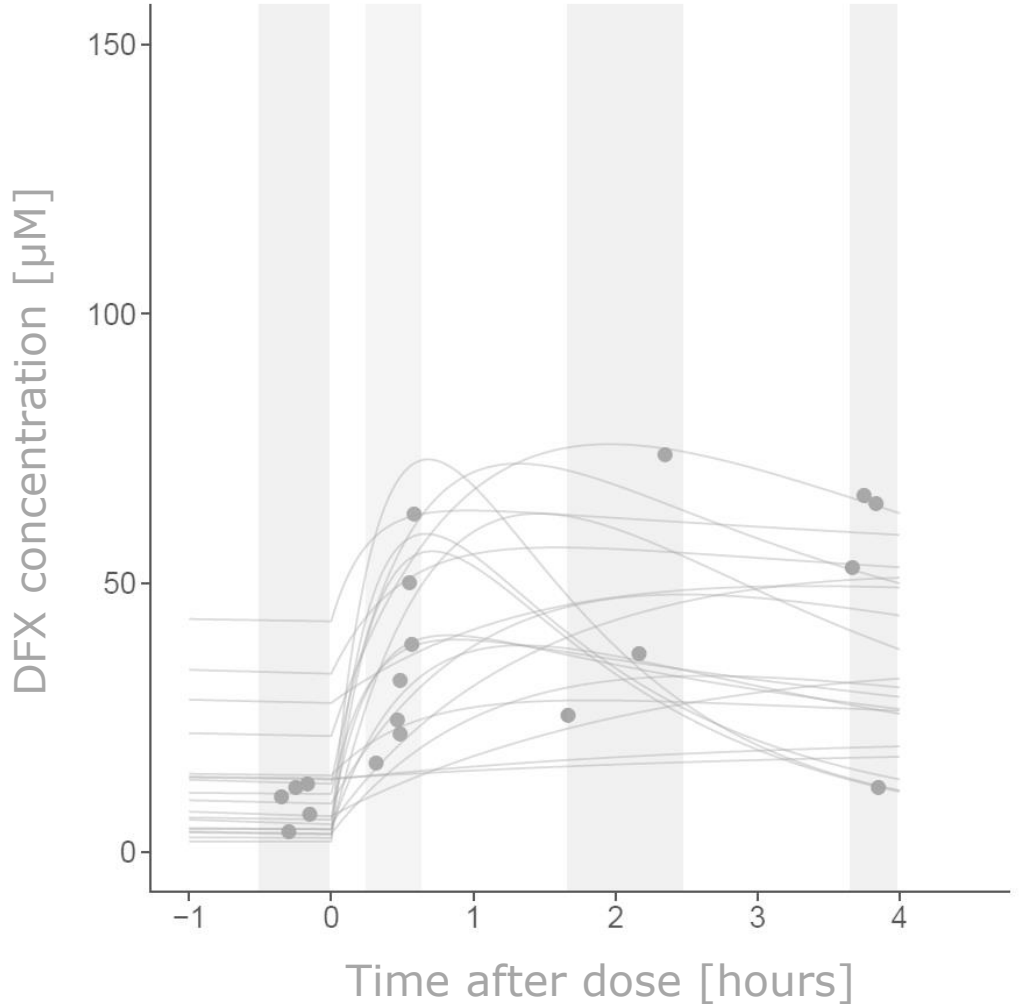

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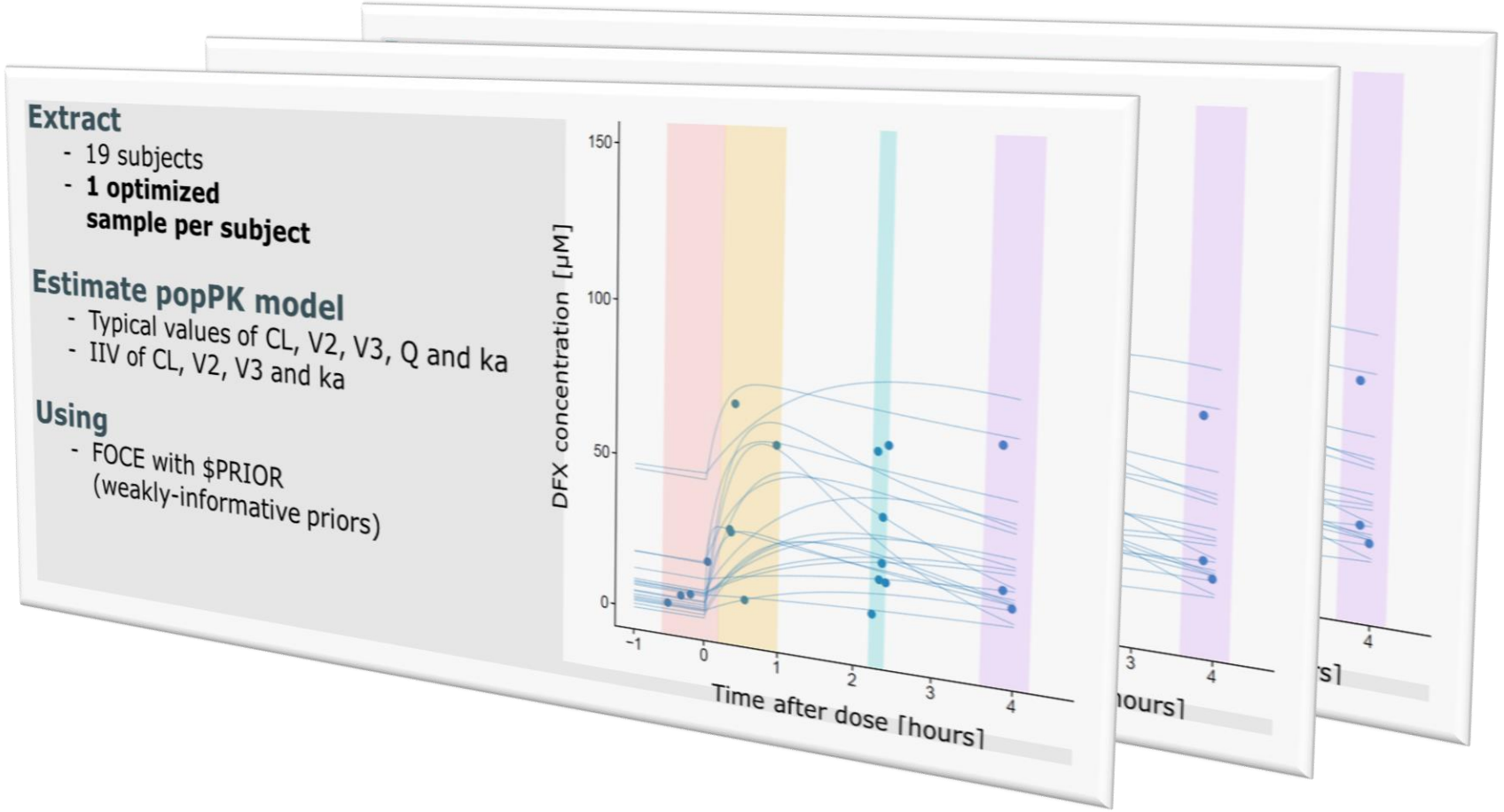
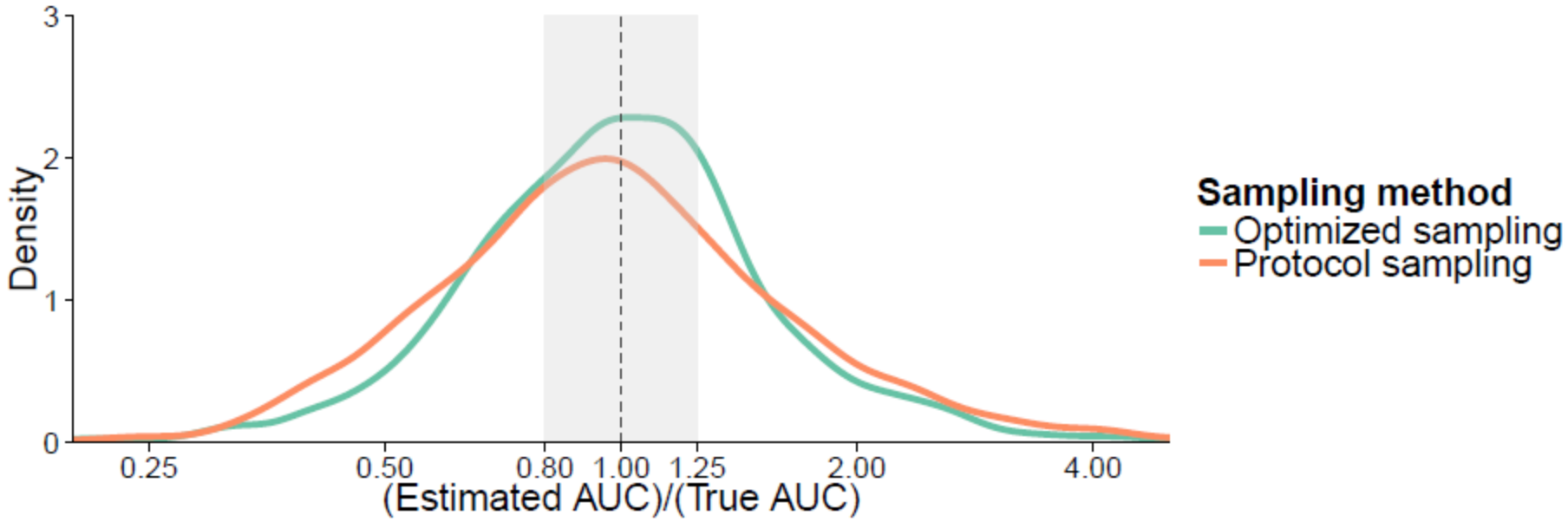
Repeat until 100 successful runs are obtained



Results

Comparison: protocol sampling vs optimized sampling (1 sample/subj)

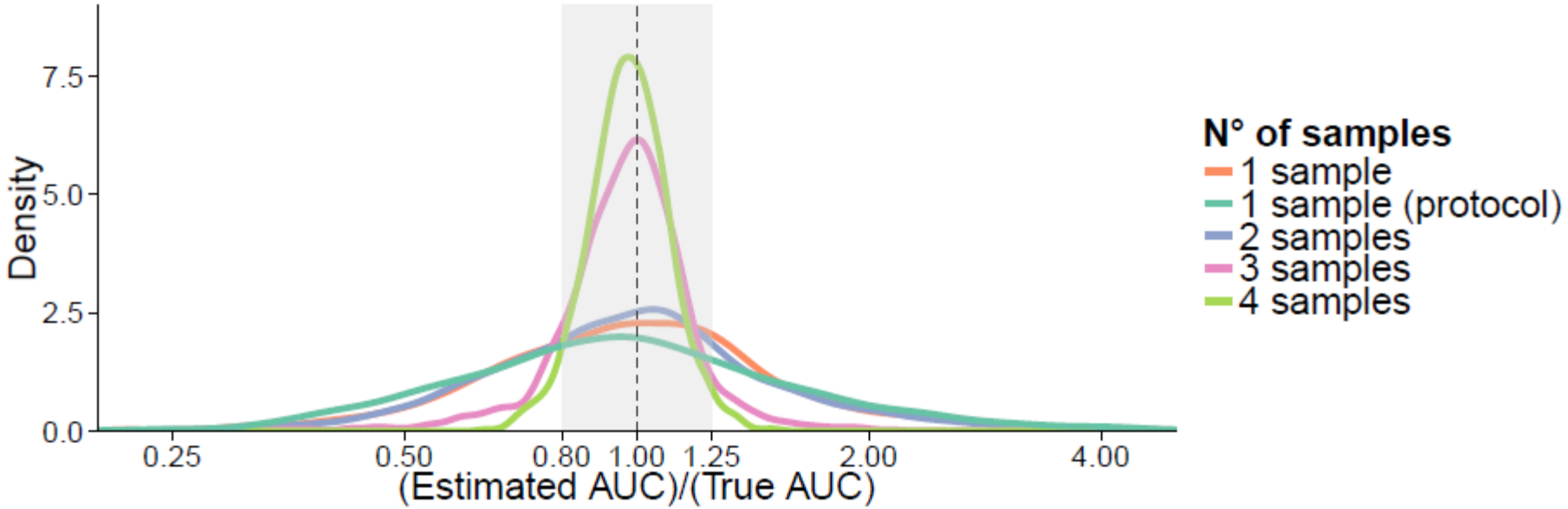
Type of sampling	N° of samples/subj	Probability of successful run (%)	Probability (%) of ratios between [0.8 ; 1.25]
Protocol sampling	1	56.50	37
Optimized sampling		51.28	42



Results

Comparison: 1 optimized sample/subj vs N optimized samples/subj (N=2,3,4)

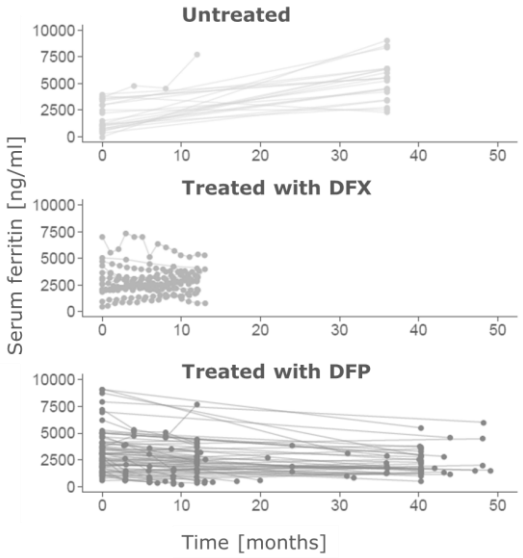
Type of sampling	N° of samples/subj	Probability of successful run (%)	Probability (%) of ratios between [0.8 ; 1.25]
Optimized sampling	1	51.28	42
	2	89.96	46
	3	92.59	82
	4	94.34	93



Objective n°3

Efficacy study earlier predicting treatment response

I. **Simulation of serum ferritin profiles** from 0 to 12 months



Transfusional iron input
(mg iron/kg/month)
[=1.6 · BLOODCONS (ml RBC/kg/month)]

$$\frac{FerMax \cdot Iron}{Fer50+Iron}$$

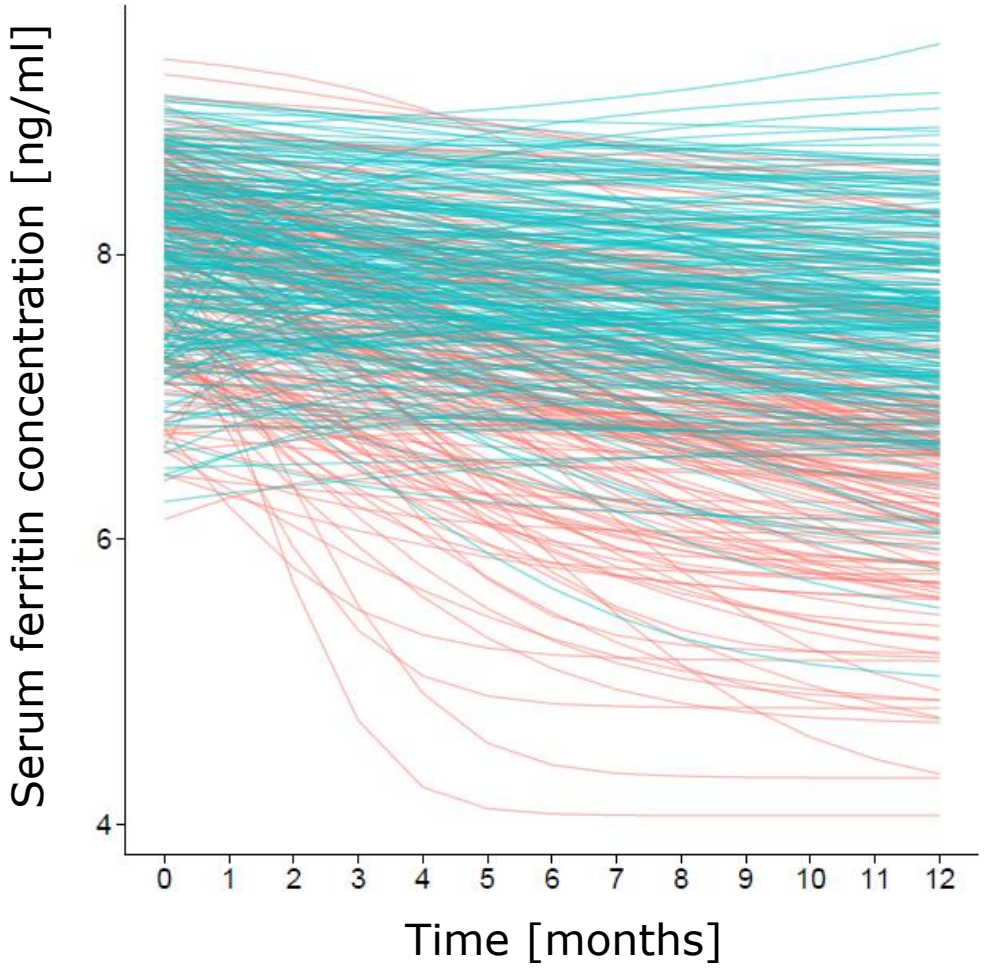
Iron → Ferritin (in plasma)

$$\frac{Iron\ (t=0) = Fer50 \cdot BASELINE}{FerMax - BASELINE}$$

$$D_{eff} = Slope \cdot C_{ss}^{av}$$

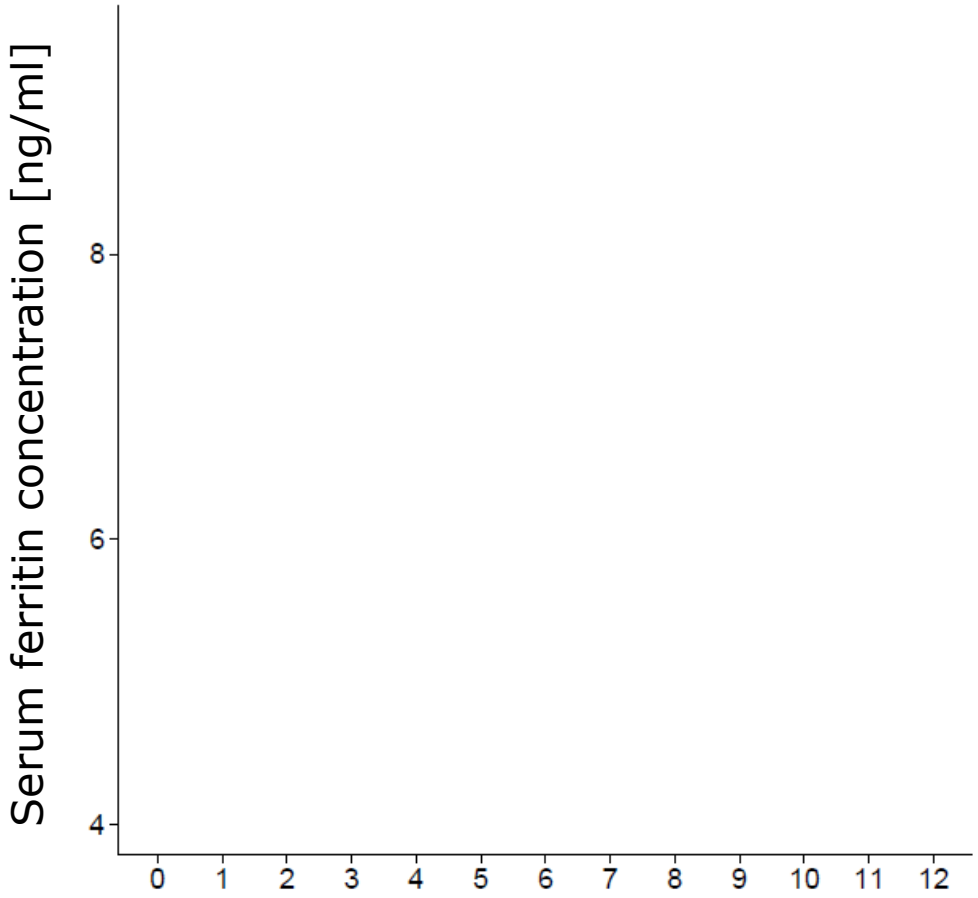
+ **Dose DFX**: 20-40 mg/kg/day
+ **Dose DFP**: 75-100 mg/kg/day

+ DEEP-2 study patients covariates
  - BLOODCONS: 150-200 ml/kg/year
  - BASELINE: 800-6000 ng/ml
  - Weight



2. Prediction of ferritin response at 12 months

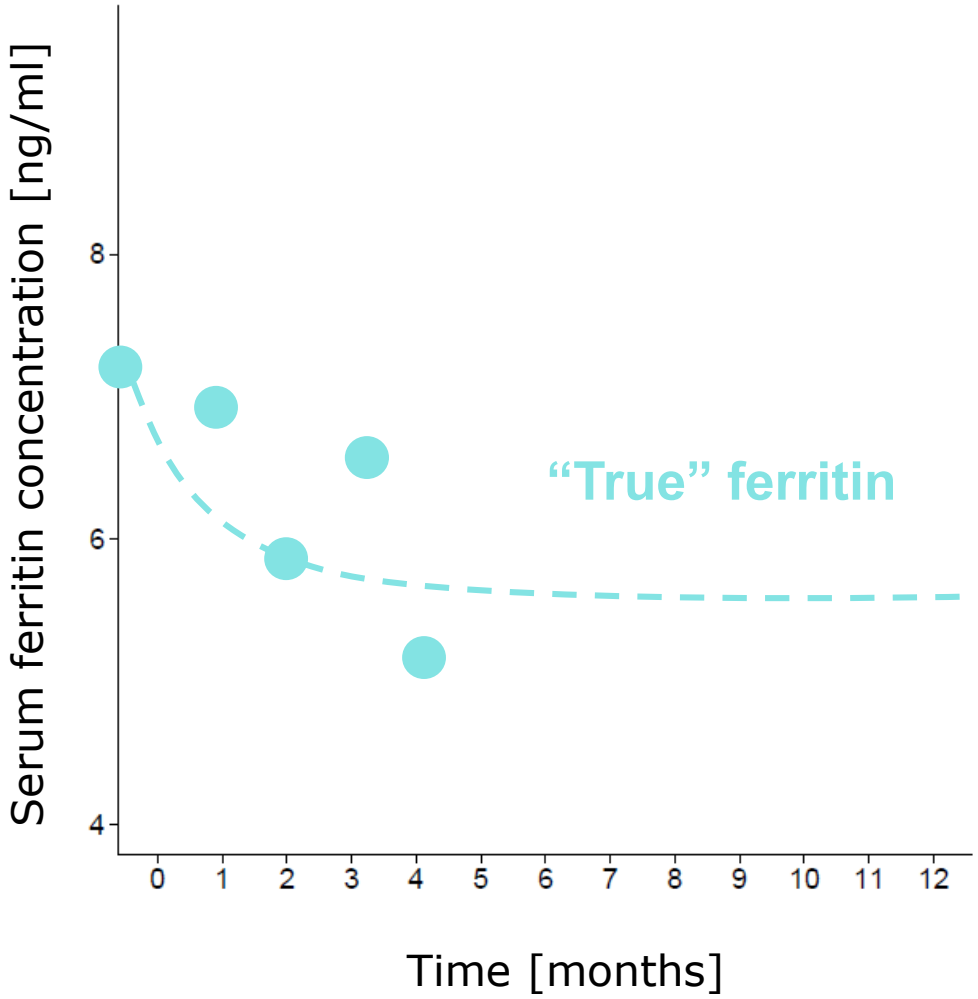
after different treatment durations (from 1 to 11 months)



2. Prediction of ferritin response at 12 months
after different treatment durations (from 1 to 11 months)

Extract for each subj

- **1 sample/month**
  until the end of the treatment

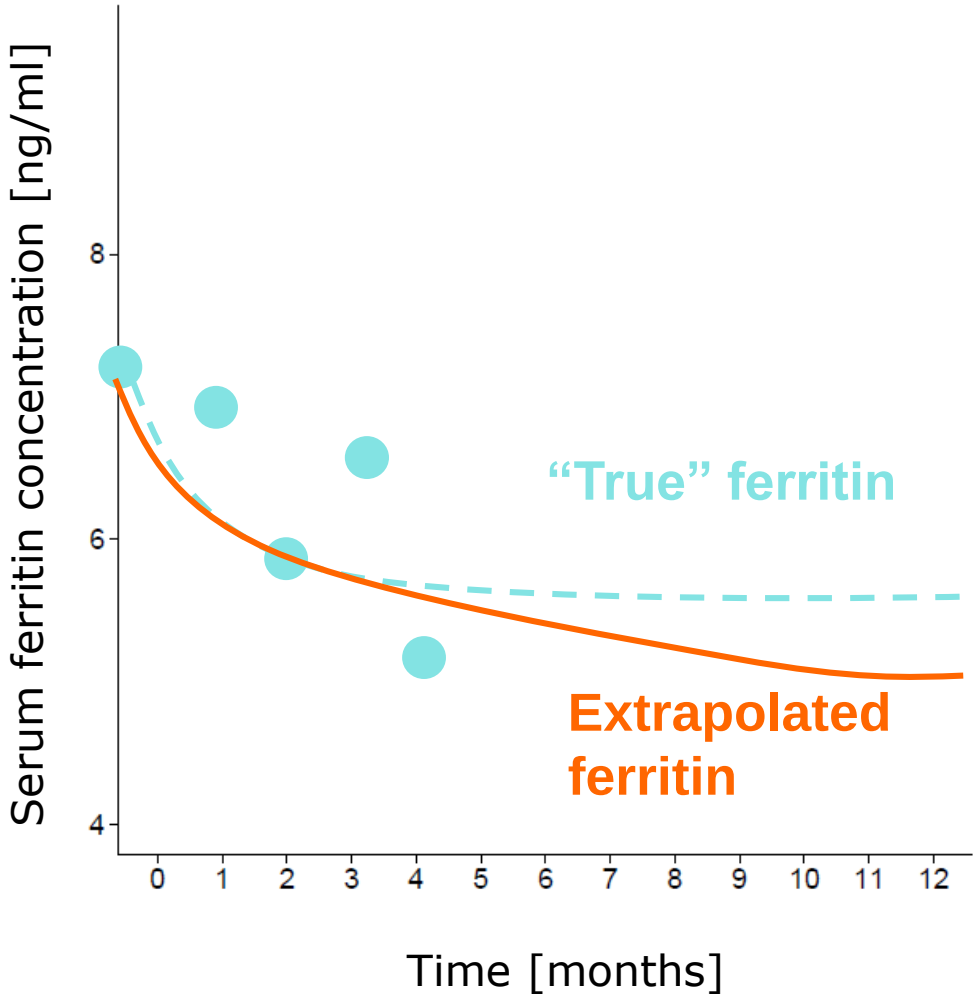


2. Prediction of ferritin response at 12 months
after different treatment durations (from 1 to 11 months)

Extract for each subj
- **1 sample/month**
  until the end of the treatment

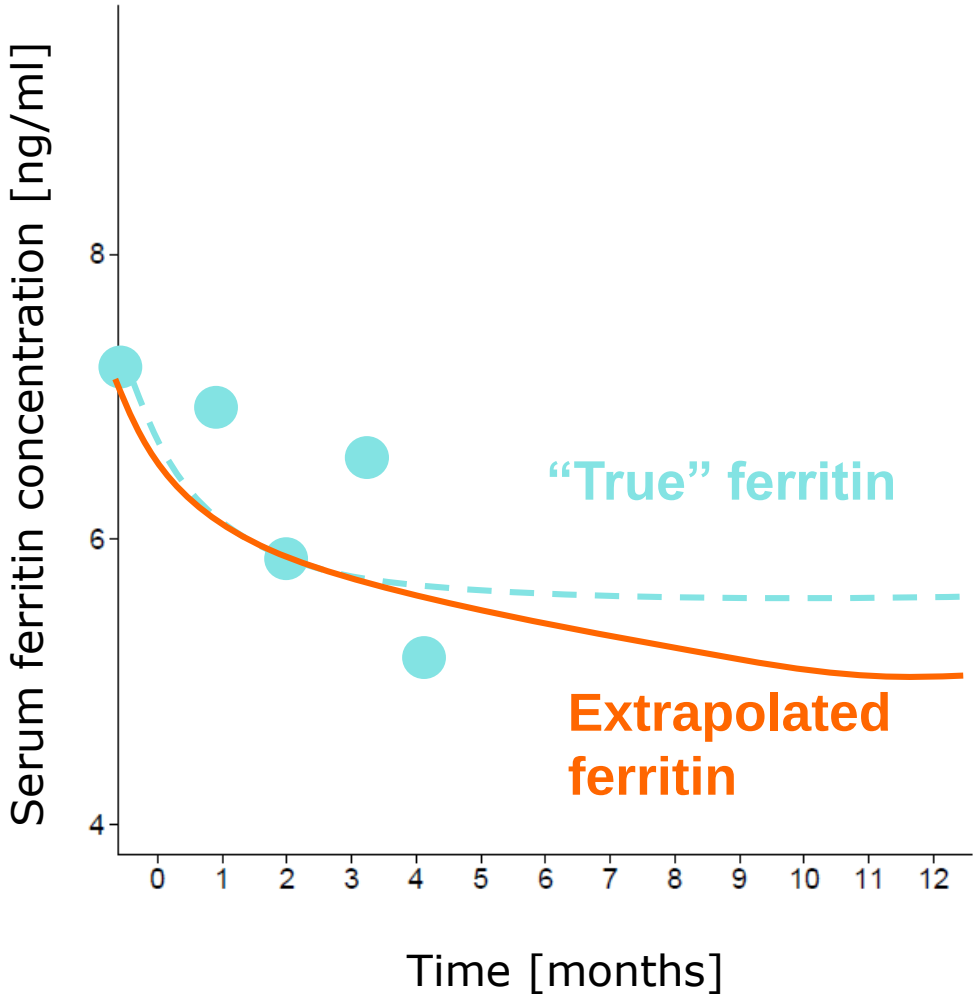
Post-hoc estimation of popPK-PD model

Extrapolate at 12 months



3. Classify patients according to their true and extrapolated values and the criteria specified in the protocol

		ACTUAL	
		Success (+)	**Not success (-)**
PREDICTED	Success (+)	TP	FP
	Not success (-)	FN	TN



3. Classify patients according to their true and extrapolated values and the criteria specified in the protocol

		ACTUAL	
		Success (+)	**Not success (-)**
PREDICTED	Success (+)	TP	FP
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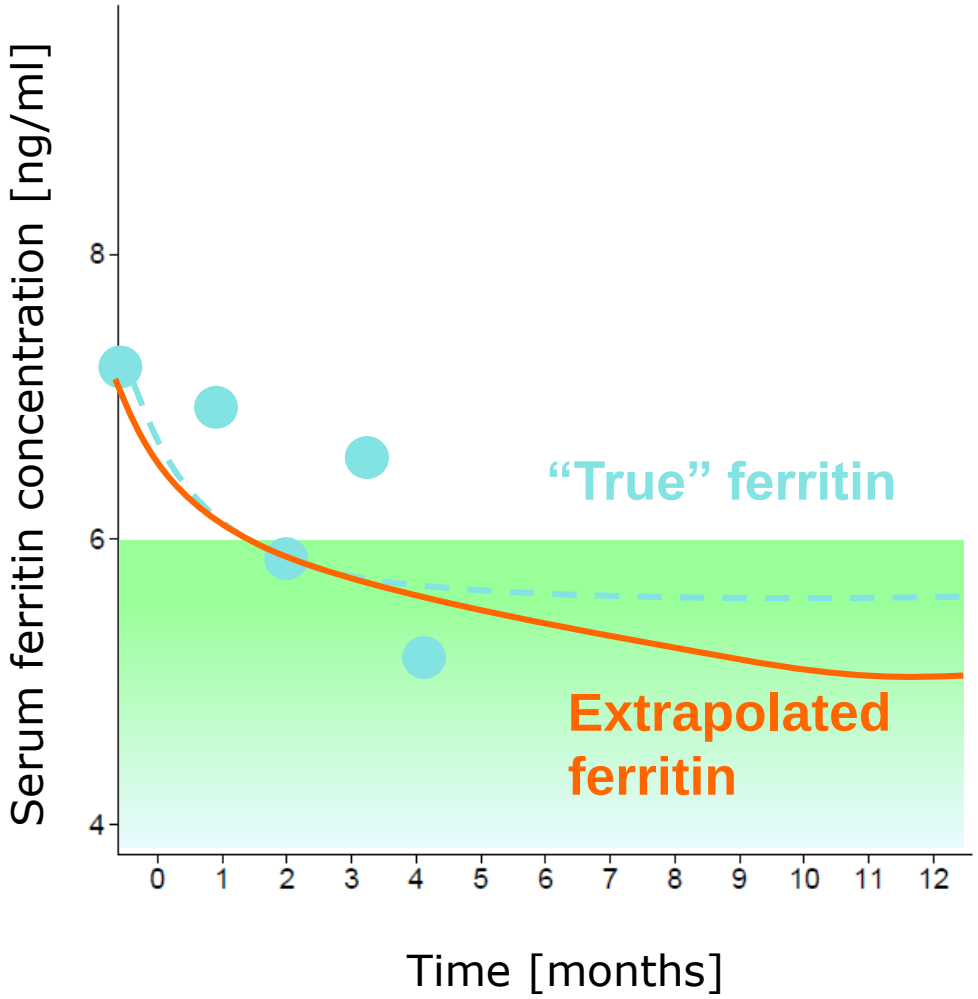

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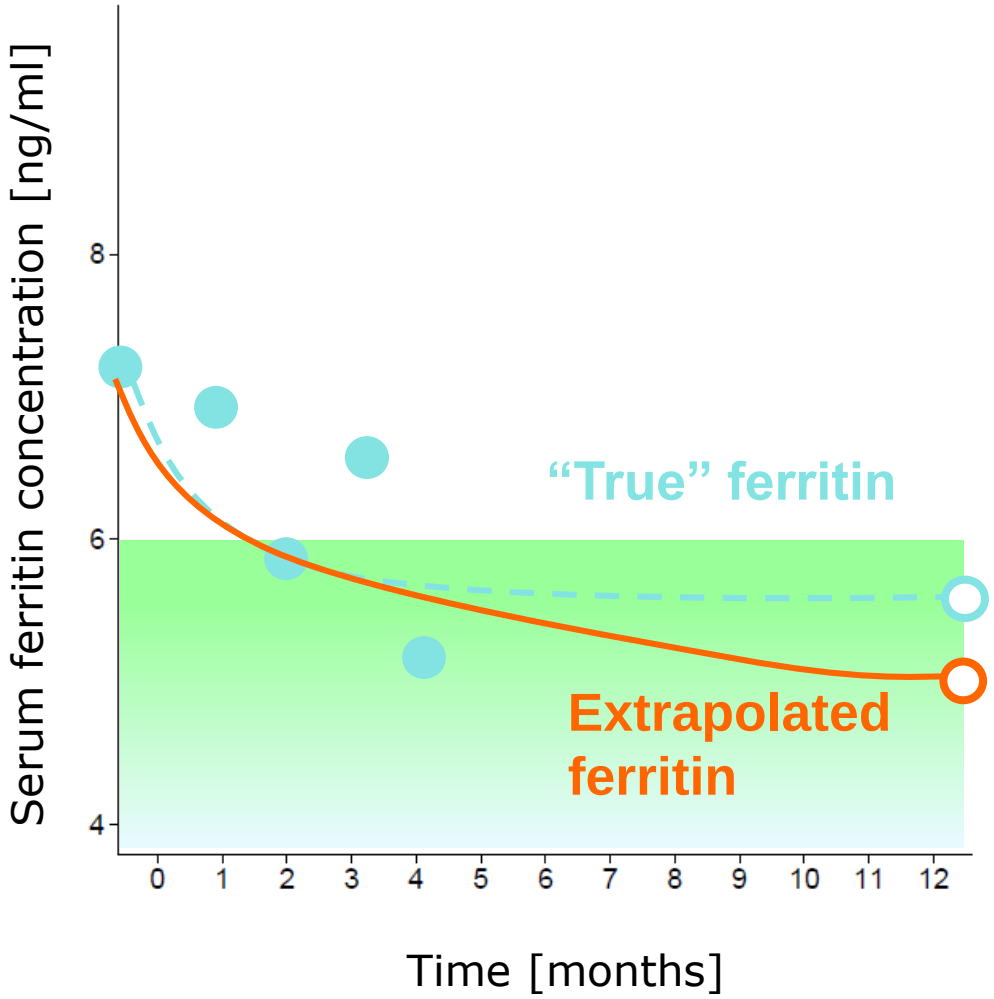
PREDICTED \ ACTUAL	Success (+)	Not success (-)
Success (+)	TP	FP
Not success (-)	FN	TN



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		ACTUAL	
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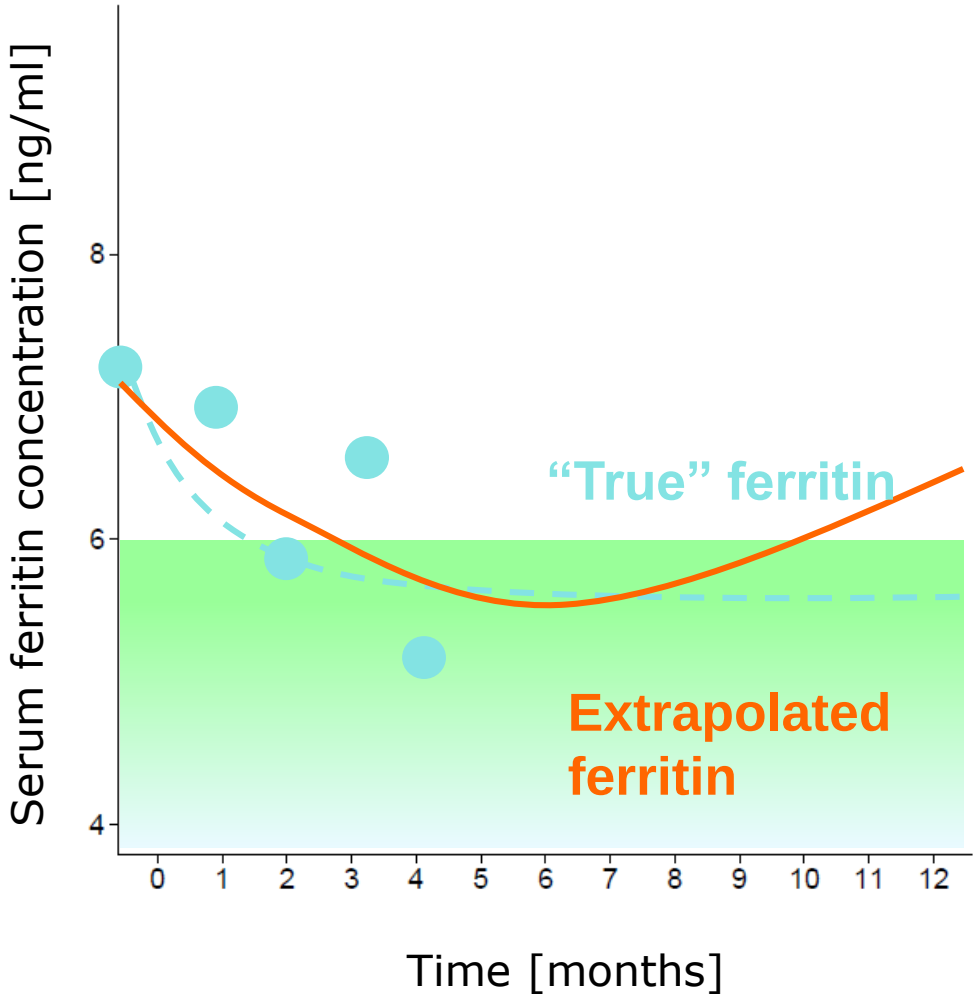

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Success (+)	TP	FP
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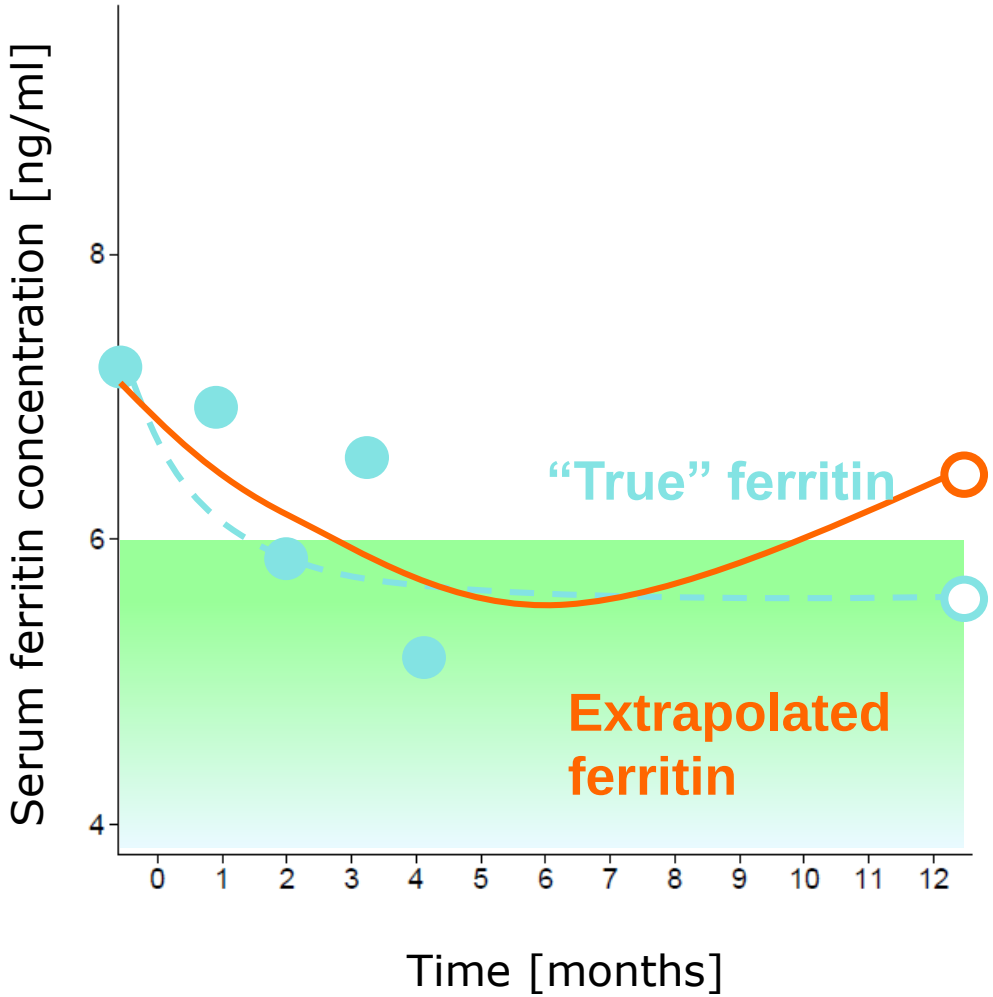
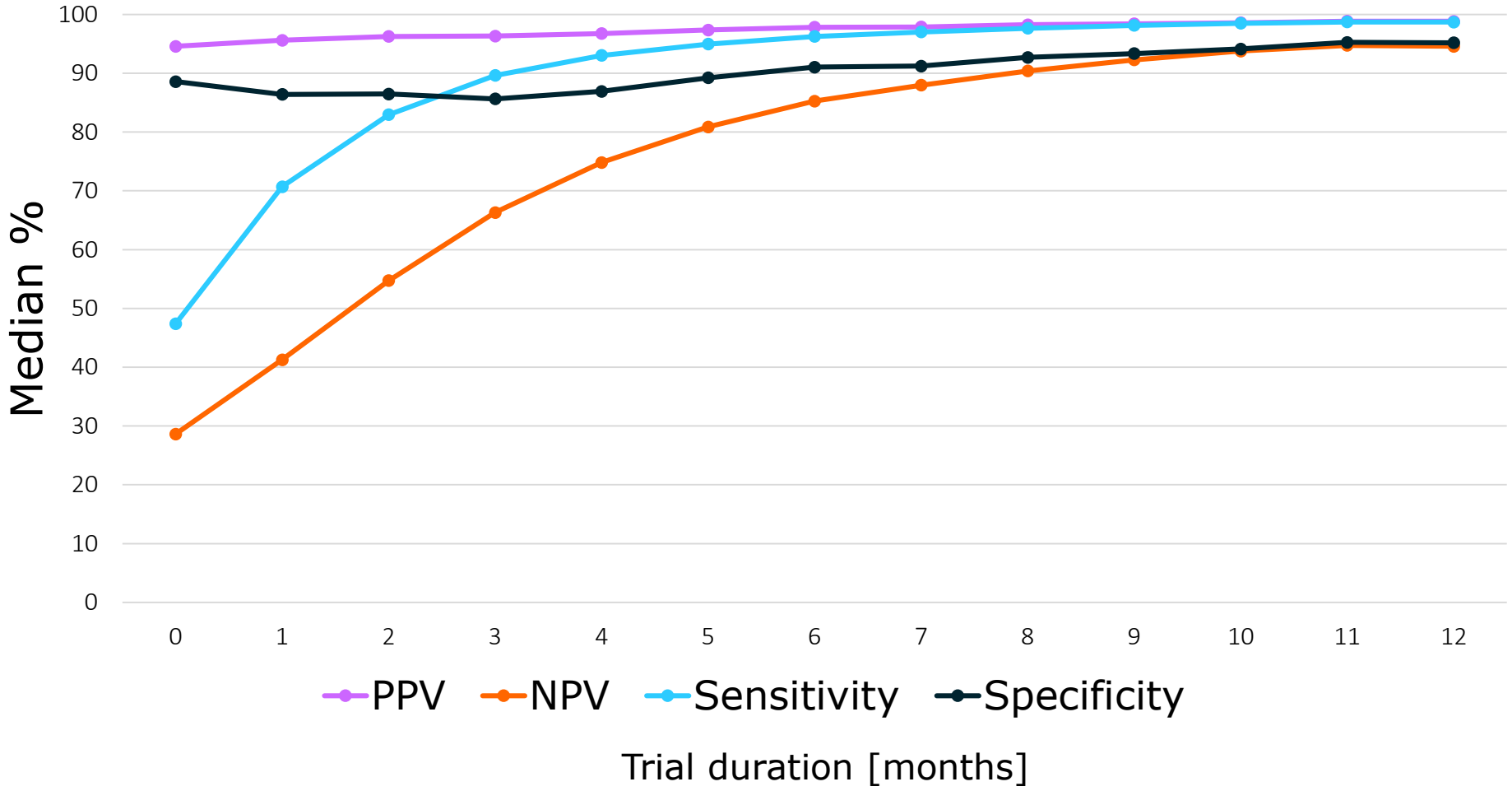


Results

Extrapolated efficacy outcome *vs* true efficacy outcome



$$PPV = \frac{TP}{TP+FP}$$

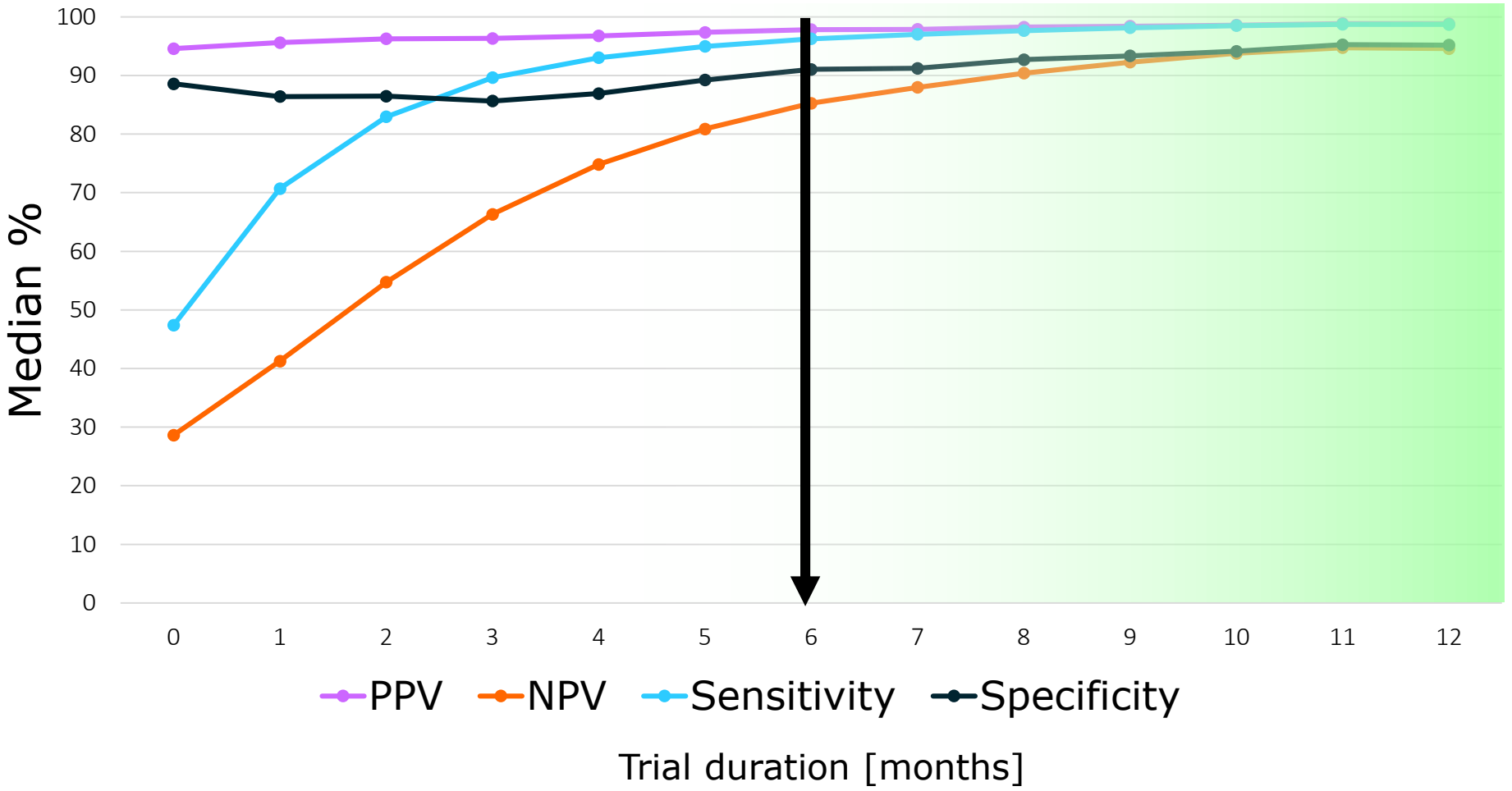
$$NPV = \frac{TN}{TN+FN}$$

$$Sensitivity = \frac{TP}{TP+FN}$$

$$Specificity = \frac{TN}{TN+FP}$$

Results

Extrapolated efficacy outcome *vs* true efficacy outcome



$$PPV = \frac{TP}{TP+FP}$$

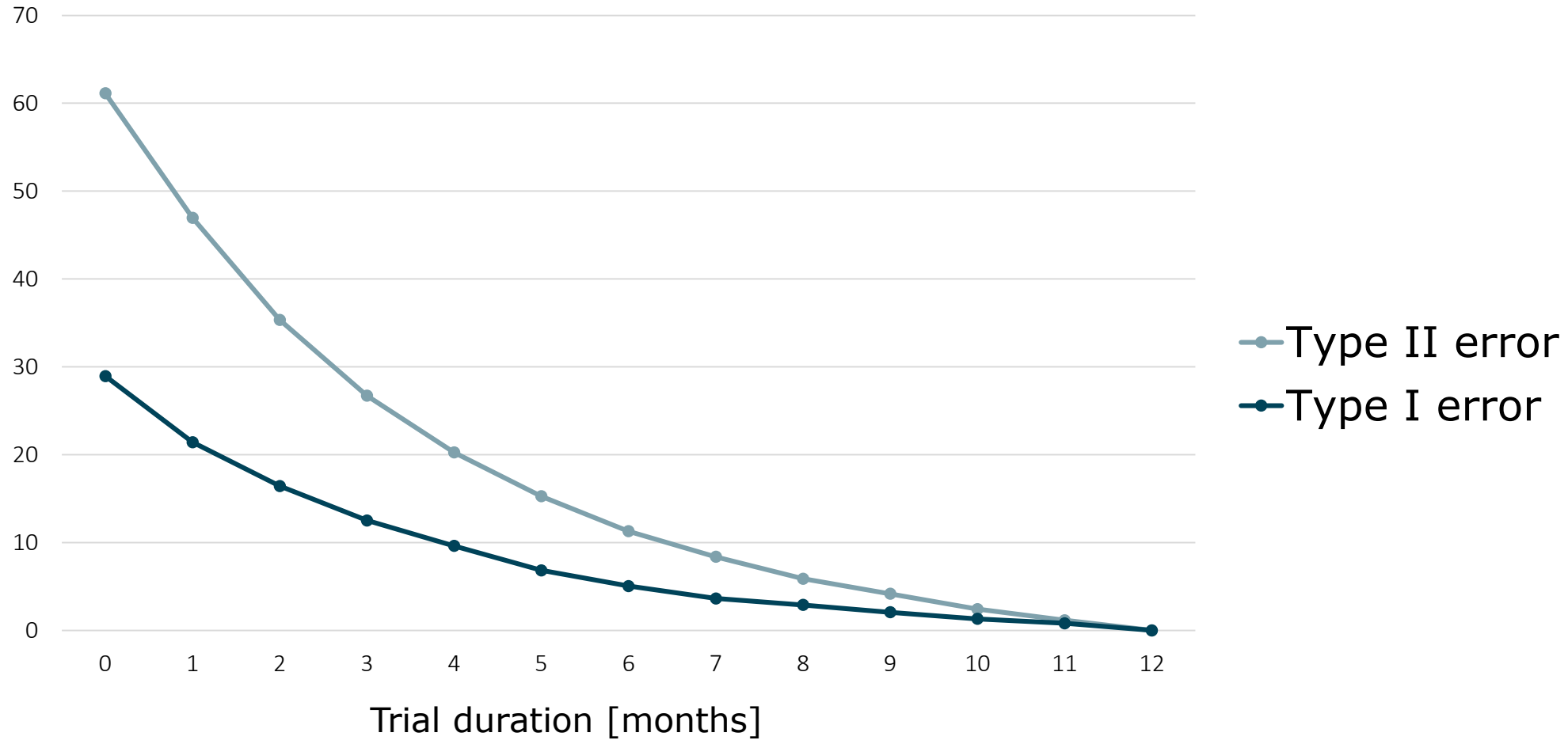
$$NPV = \frac{TN}{TN+FN}$$

$$Sensitivity = \frac{TP}{TP+FN}$$

$$Specificity = \frac{TN}{TN+FP}$$

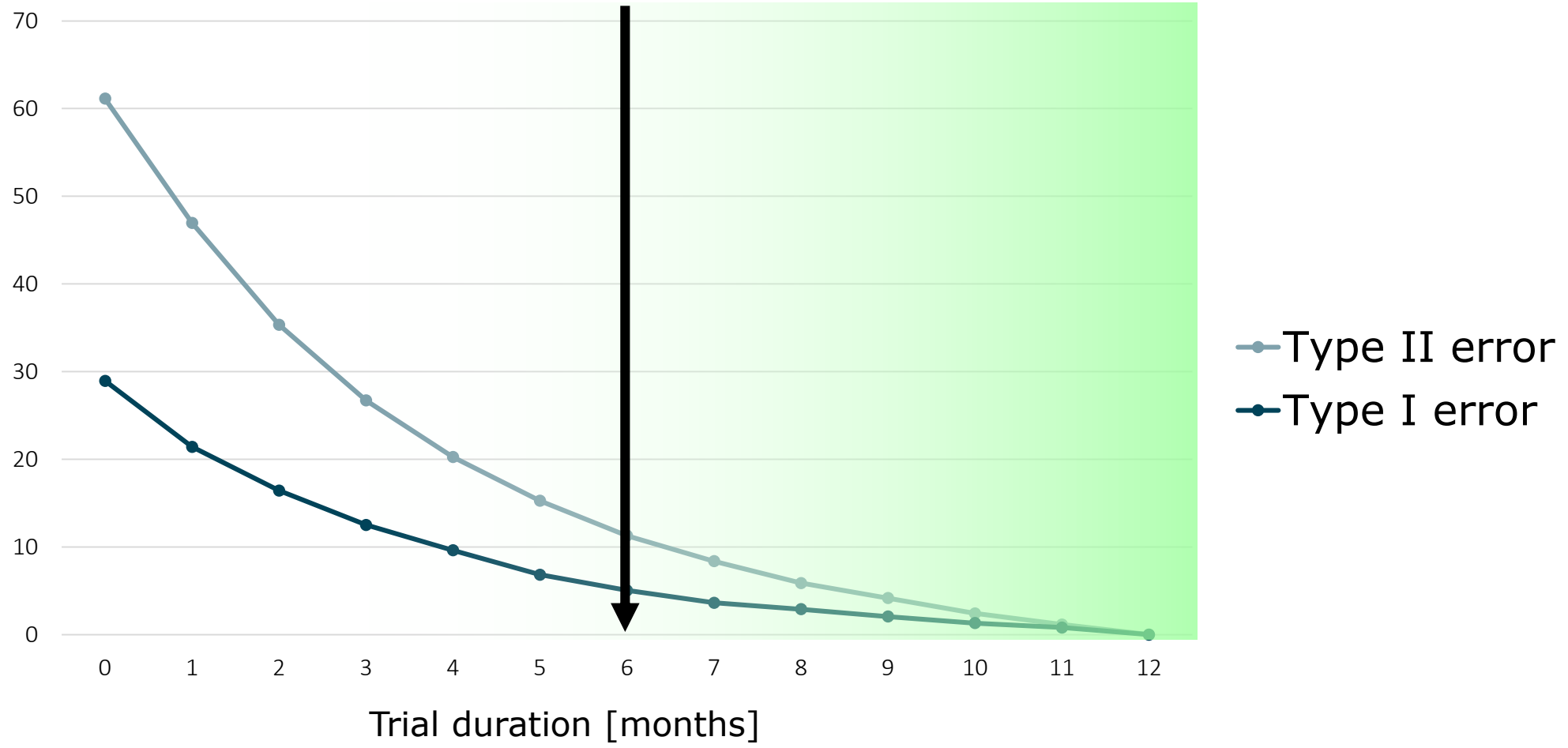
Results

True efficacy outcome at the end of the treatment *vs* true efficacy outcome at 12 months



Results

True efficacy outcome at the end of the treatment *vs* true efficacy outcome at 12 months



Summary

- Priors increases dramatically the probability of successful convergence of the FOCE-I method
- One sample per subject, even if optimized, leads to a 60% chance of over/underestimating the exposure
- Increasing the number of samples from 1 to 3 shrinks this probability to less than 10%
- The use of a model-based meta-analytical approach leads to predictive performances (e.g., PPV) at 6 months that are not significantly different from those at 1 year, suggesting the possibility of shorter trial duration

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DEEP project

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DEferiprone Evaluation in Paediatrics

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