Pediatric Drug Development Workshop

October 28-29 | Bethesda, MD

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The use of modeling & simulation to facilitate an understanding of pediatric dose-exposure-response for small molecules and biologics.

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Key Questions in Pediatric Pharmacology: M&S Opportunities

Is the pediatric disease similar to adult disease?

- Quantitative Systems Pharmacology Models

What is the relationship between dose and exposure in children?

- (Population) Pharmacokinetic Models

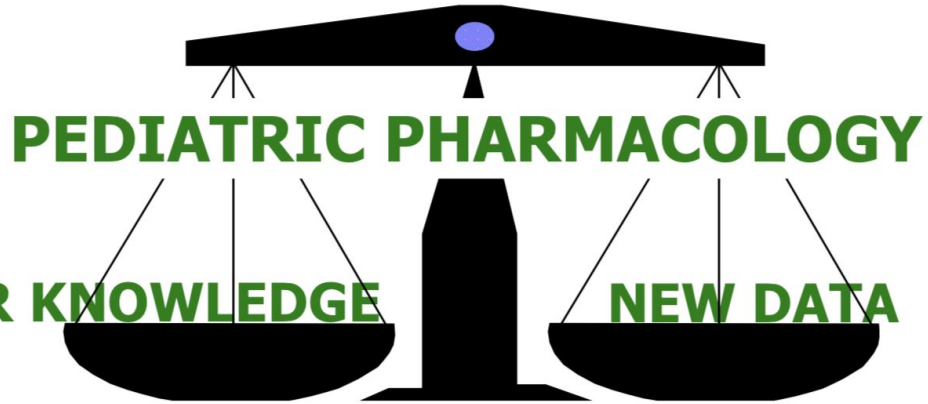
What is the relationship between exposure and response in children?

- Pharmacokinetic-Pharmacodynamic Models

Will a pediatric trial meet stated goals & learnings?

- Clinical Trial Simulation

Bayesian Modeling Methods in Pediatrics



- Adult model and parameters
- Link between pediatric and adult PK-PD, efficacy, toxicity
- Prior knowledge of (patho)physiology, therapeutic area

- New PK-PD, efficacy, toxicity data from pediatric patients

$$p(\theta|Y) = \frac{p(\theta)\,p(Y|\theta)}{p(Y)}$$

Thomas Bayes. An essay towards solving a problem in the doctrine of chances, (1764).

INFLUENTIAL FACTORS

- Magnitude of inter-individual variability
- Quality of data (residual/measurement error)
- Quantity of new data (no. of individuals & data points)
- Uncertainty in prior model and parameters

Exposure-Matching to Support Extrapolation

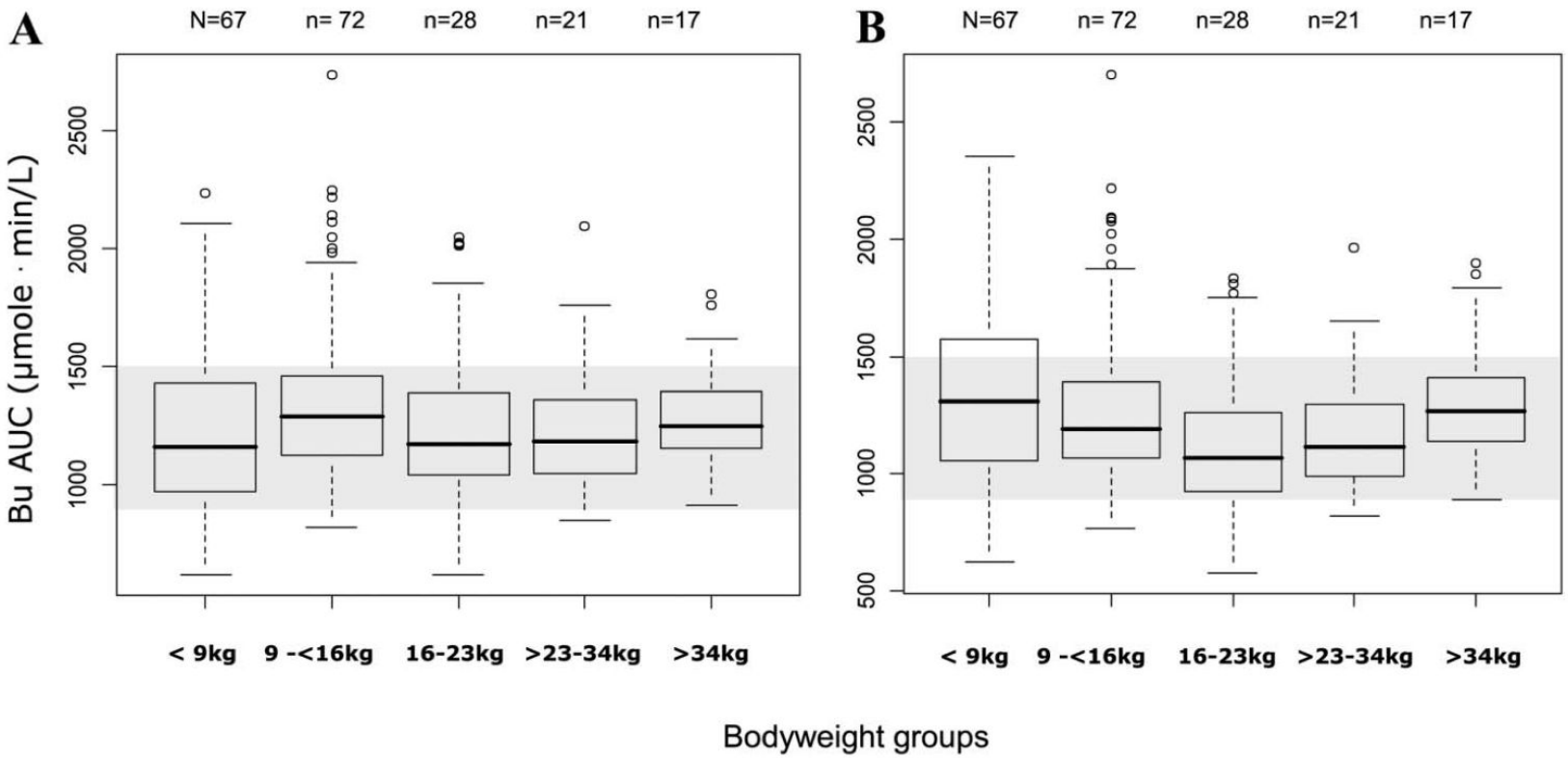


FIGURE 5. Comparison of dosing strategy between model-based and EU labeled dosing. A, Bu AUC distribution using approved EU labeling dosing. B, Bu AUC distribution using model-based dosing.

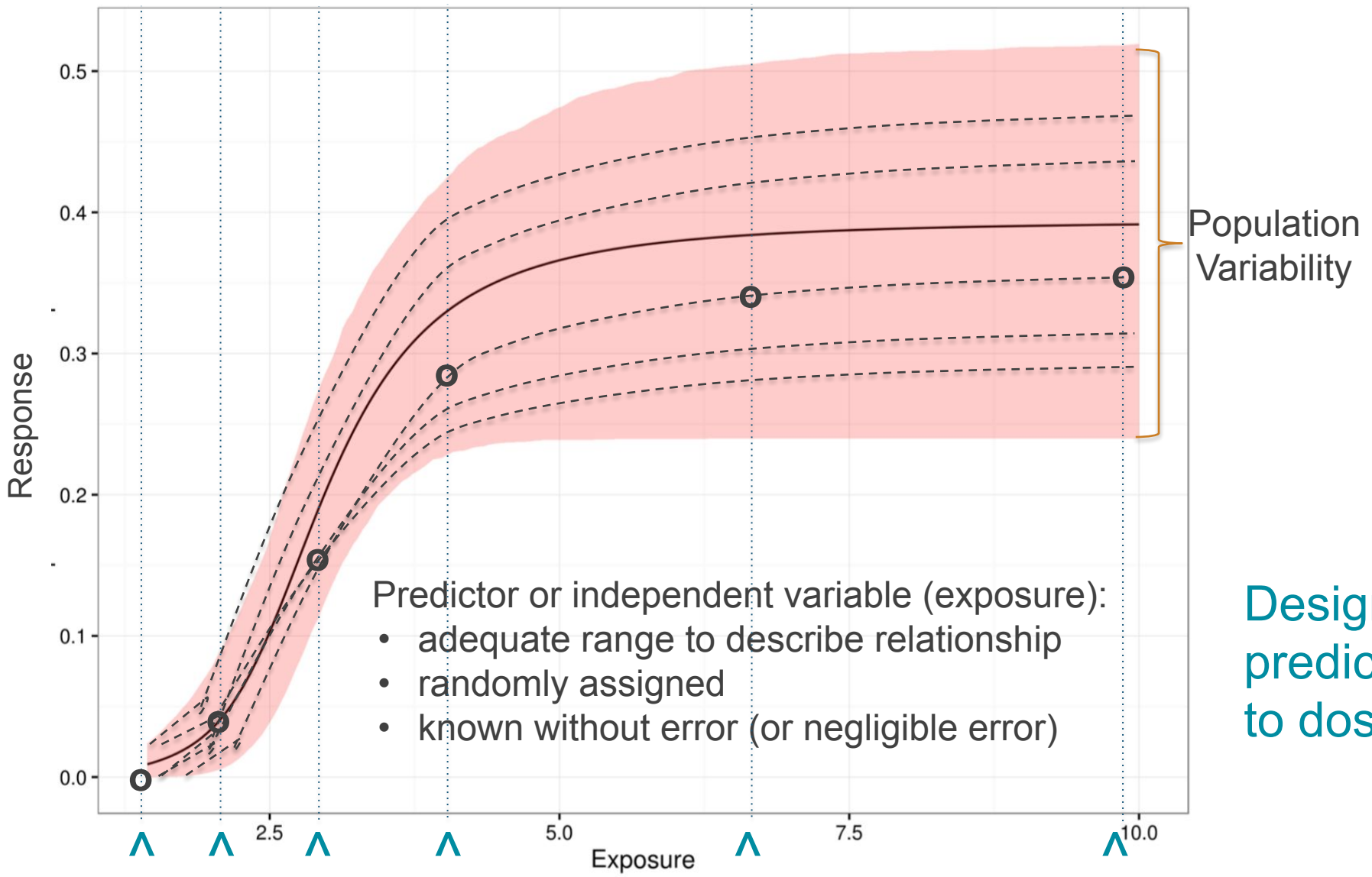
Paci et al. Pharmacokinetic Behavior and Appraisal of Intravenous Busulfan Dosing in Infants and Older Children: The Results of a Population Pharmacokinetic Study From a Large Pediatric Cohort Undergoing Hematopoietic Stem-Cell Transplantation. Ther Drug Monit 2012;34:198–208.

Guidance for Industry

Exposure-Response Relationships — Study Design, Data Analysis, and Regulatory Applications

- "A dose-response study is one kind of adequate and well-controlled trial that can provide primary clinical evidence of effectiveness."
- "Exposure-response information can support the primary evidence of safety and/or efficacy."
- "In general, the more critical a role that exposure-response information is to play in the establishment of efficacy, the more critical it is that it be derived from an adequate and well controlled study (see 21 CFR 314.126), whatever endpoints are studied."

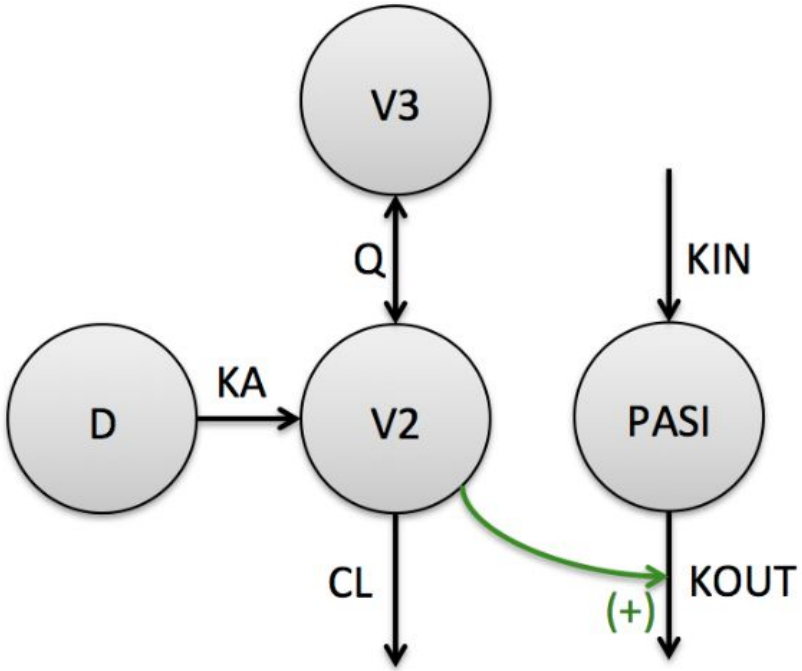
Ideal Design of Exposure-Response Studies



Design-driven range in predictor (e.g. randomized to dose or exposure) is key.

Drug and Indication

- Anti IL-17A human mAb
- Adult patients with:
  - Plaque psoriasis
  - Psoriatic arthritis
  - Ankylosing spondylitis
- Induction dose (adults):
  - 150/300 mg qw x5, then q4w



Questions

- What dose is appropriate in pediatric population?
- Should different weight groups get different doses?
  - How to compose weight groups?
  - What dose to give each group ?
- How might we conduct therapeutic drug monitoring?

Model

- Published in FDA Clin Pharm Review
  - *125504Orig1s000*
- Two-compartment PK
  - Weight is only covariate on clearances and volumes
- Endpoint is $PASI_{75}$
- Turnover-type PD model for PASI

https://www.metrumrg.com/interactive-apps-decision-making/

DIA

Interactive Simulation & Visualization w/ Cloud Computing

Shiny by RStudio

Web Browser Interface

EC2 Clusters

qapply

mrgsolve

Rcpp
C++
ODEpack

https://www.metrumrg.com/interactive-apps-decision-making/

Model Inputs

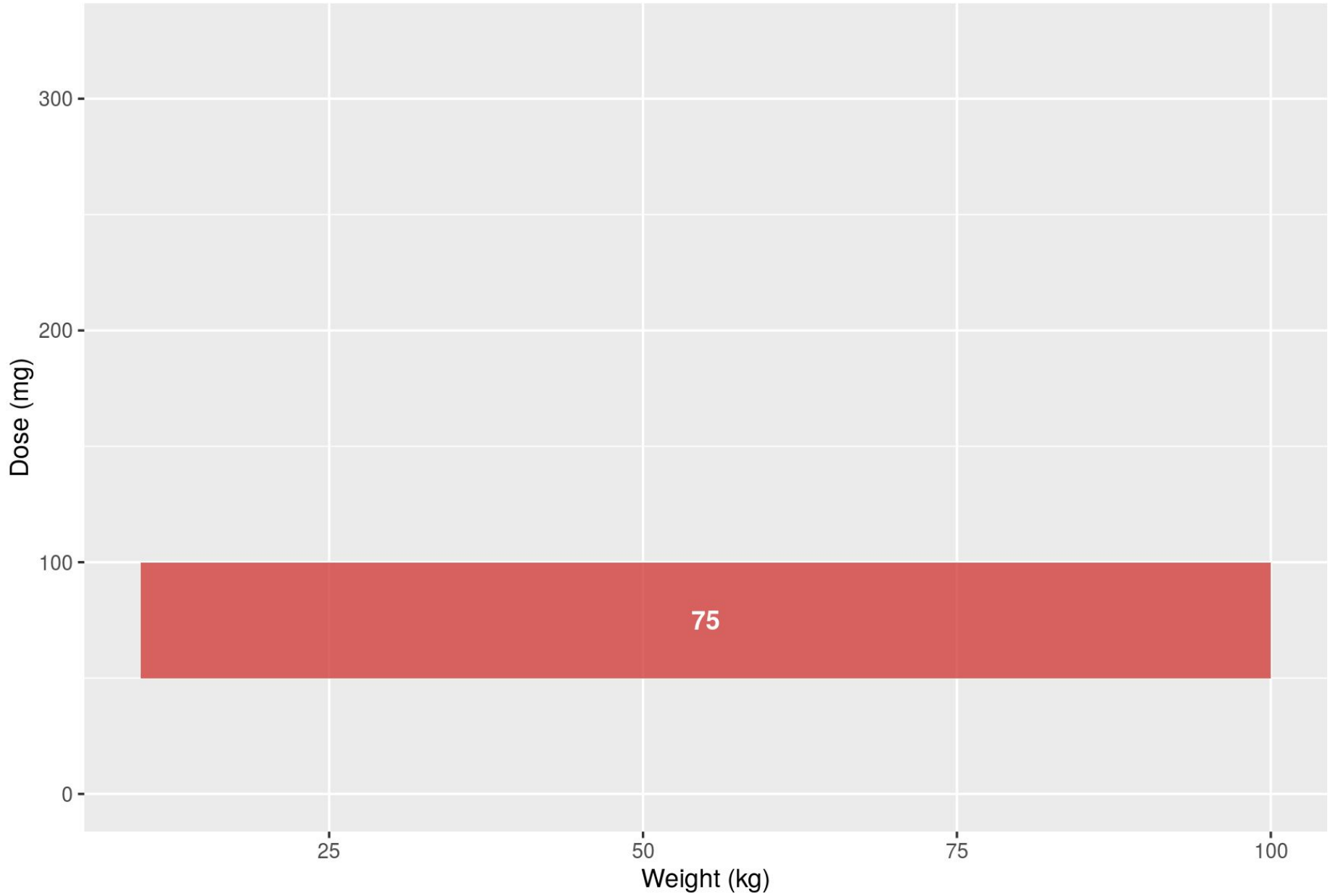
Pediatric dose (mg)

75

Weight groups (kg)

Model Results Up to Date

PROBLEM | PLAN | EXPOSURE | OUTCOME



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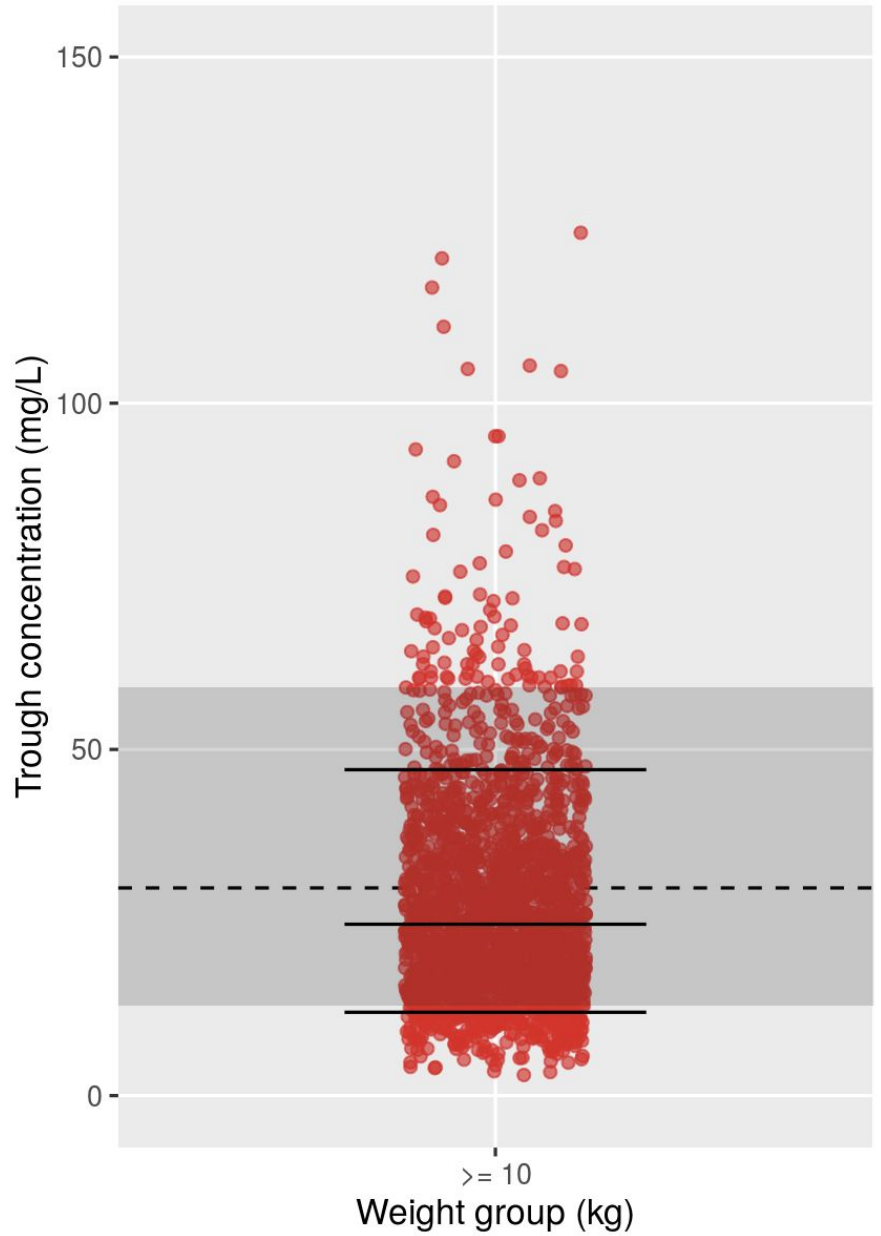

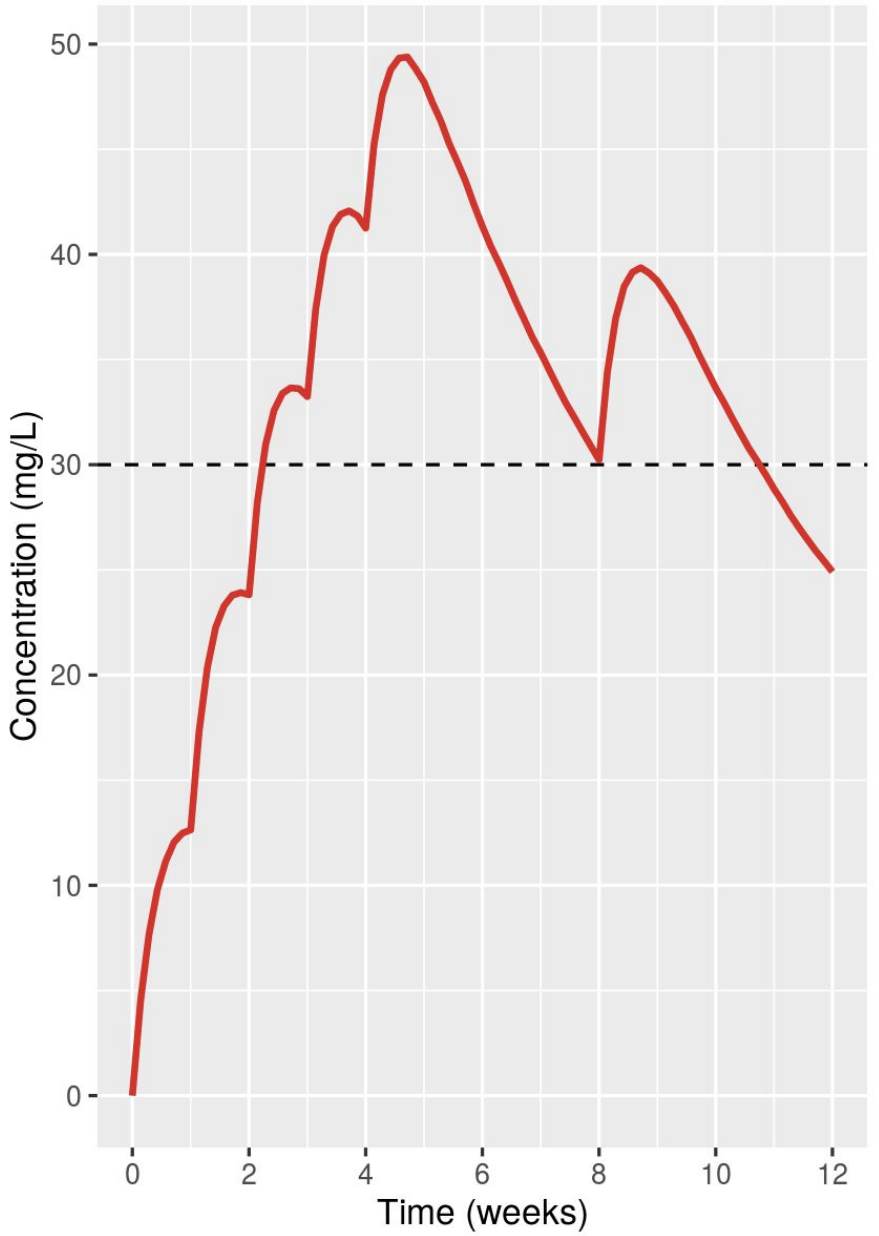

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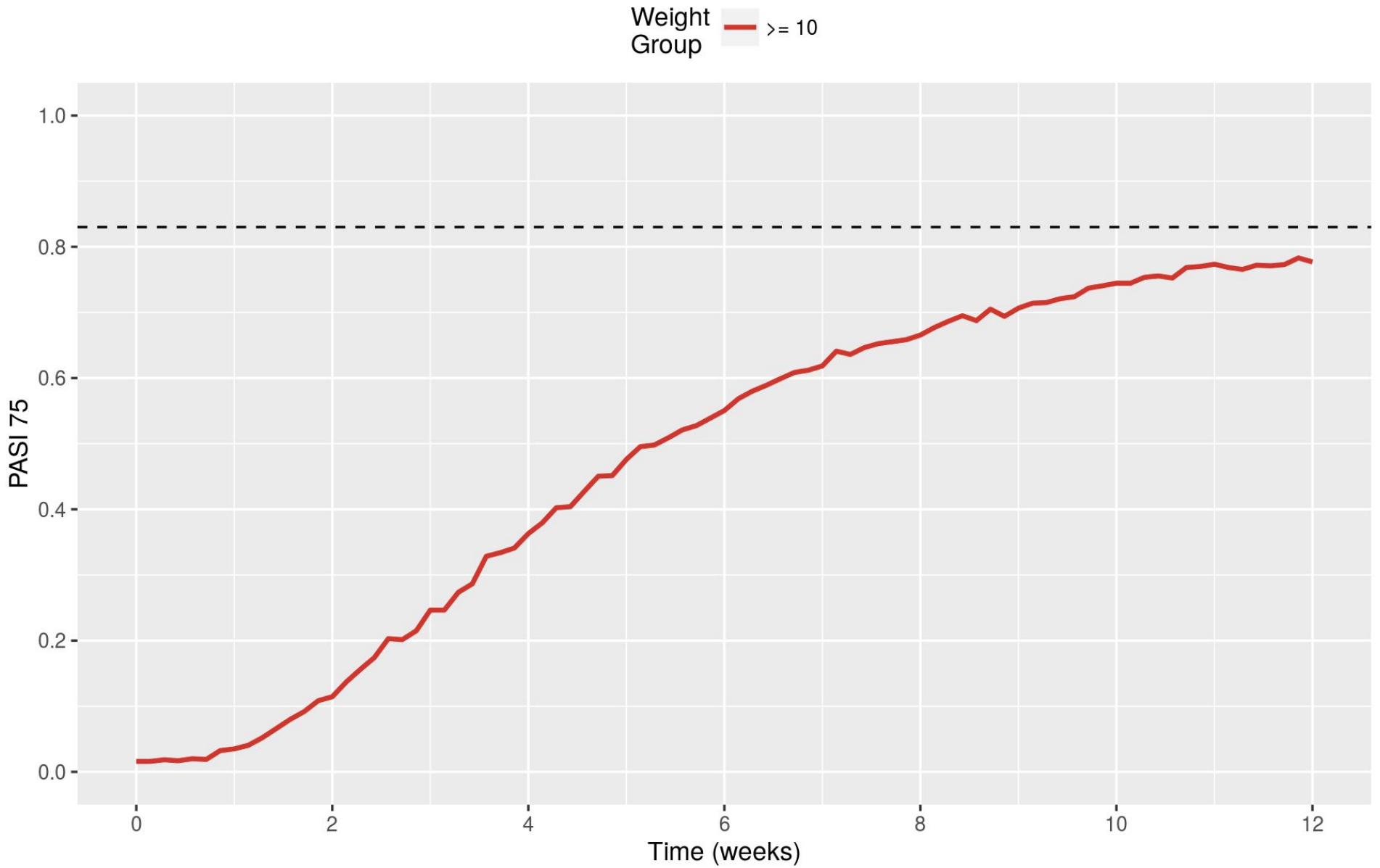


PROBLEM | PLAN | EXPOSURE | OUTCOME

Model Inputs

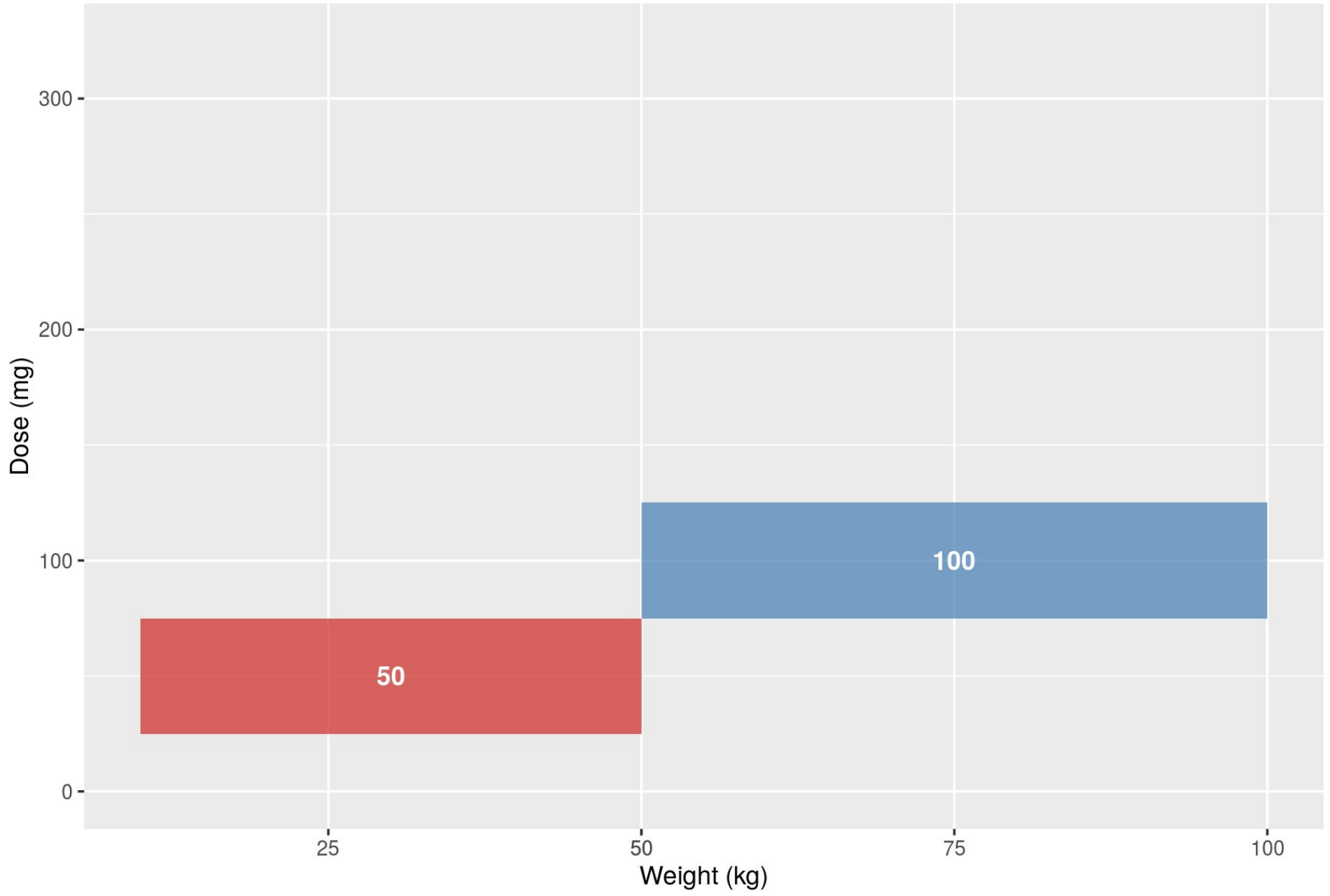
Pediatric dose (mg)

50 100

Weight groups (kg)

50

Model Results Up to Date



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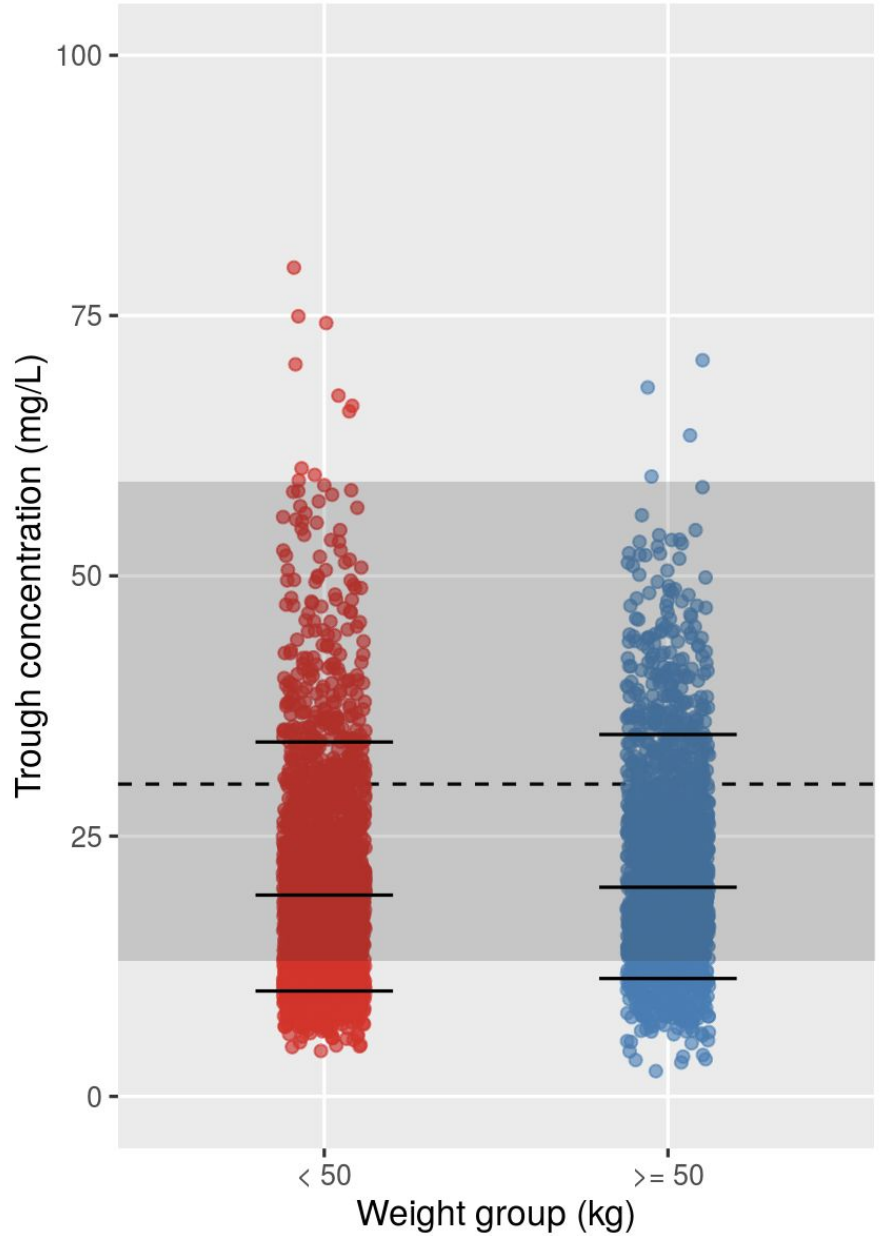

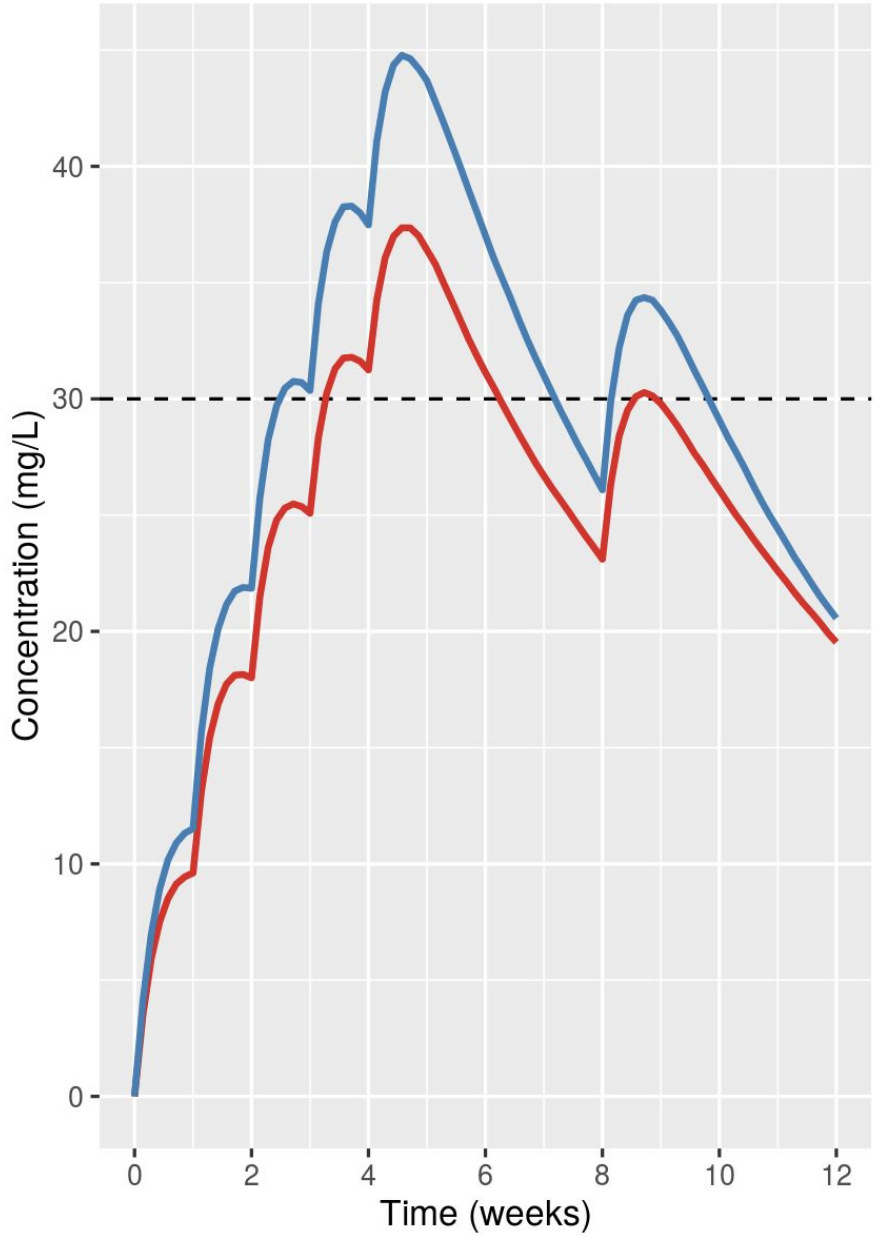

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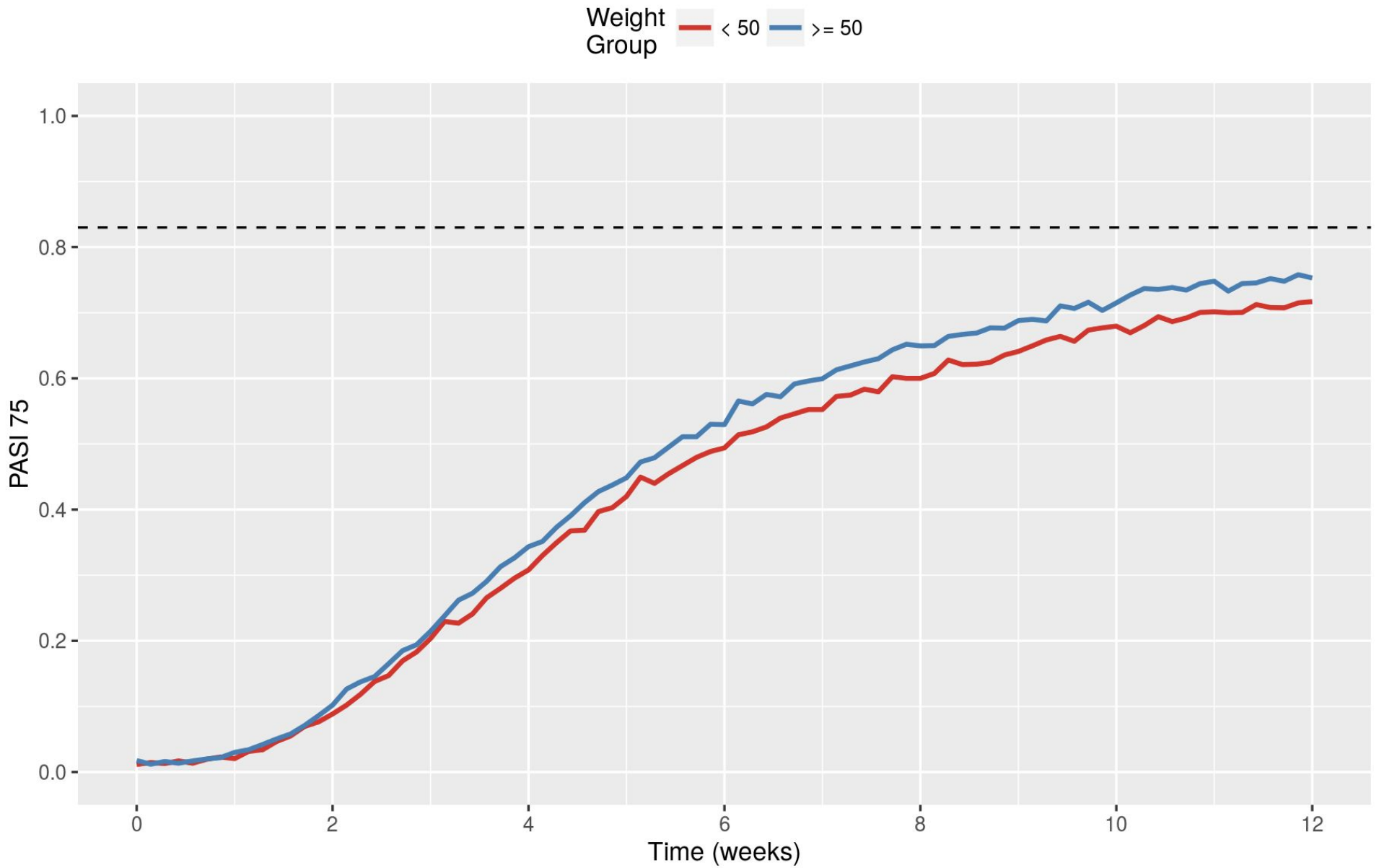

PROBLEM | PLAN | EXPOSURE | OUTCOME

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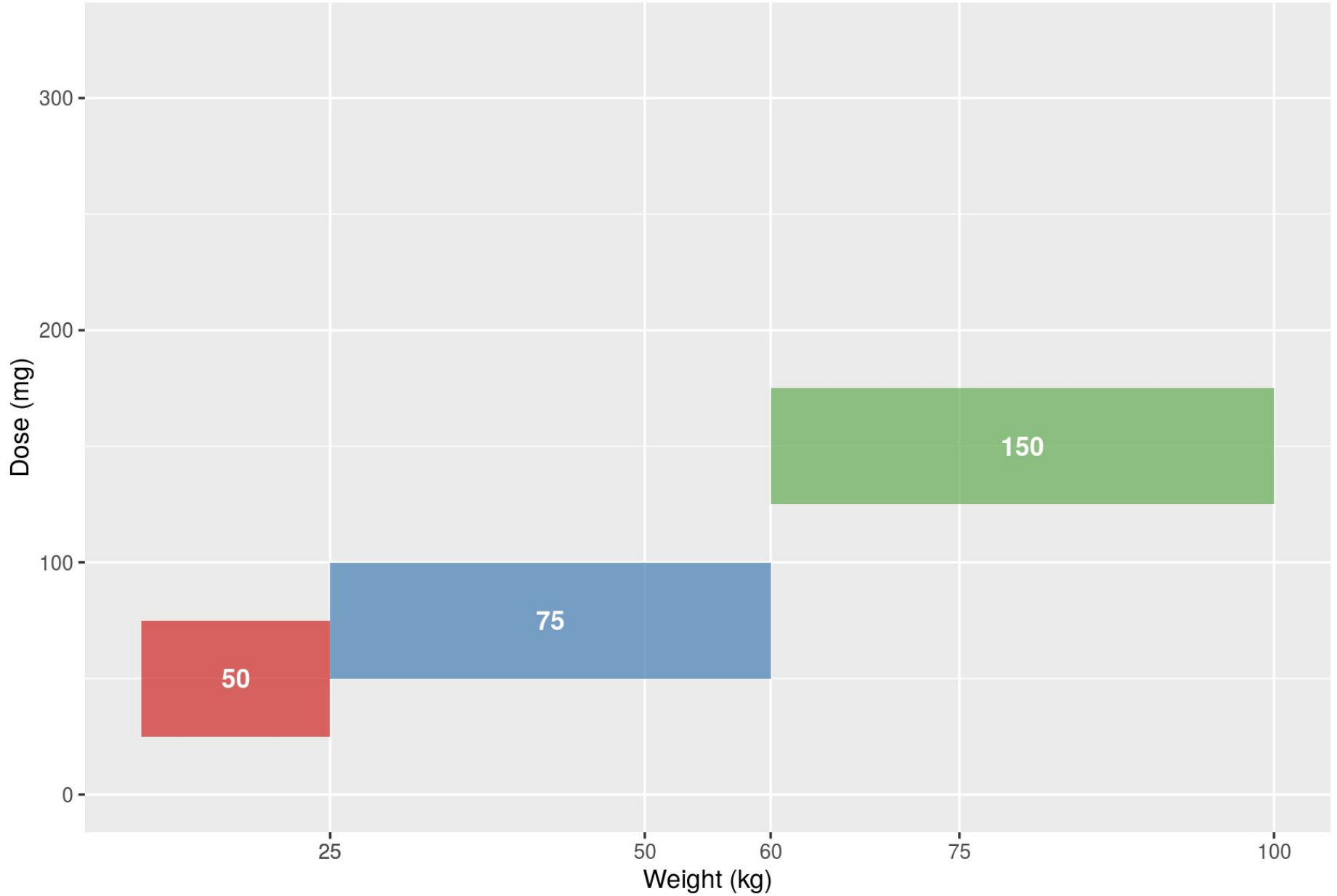
Pediatric dose (mg)

50 75 150

Weight groups (kg)

25 60

Model Results Up to Date



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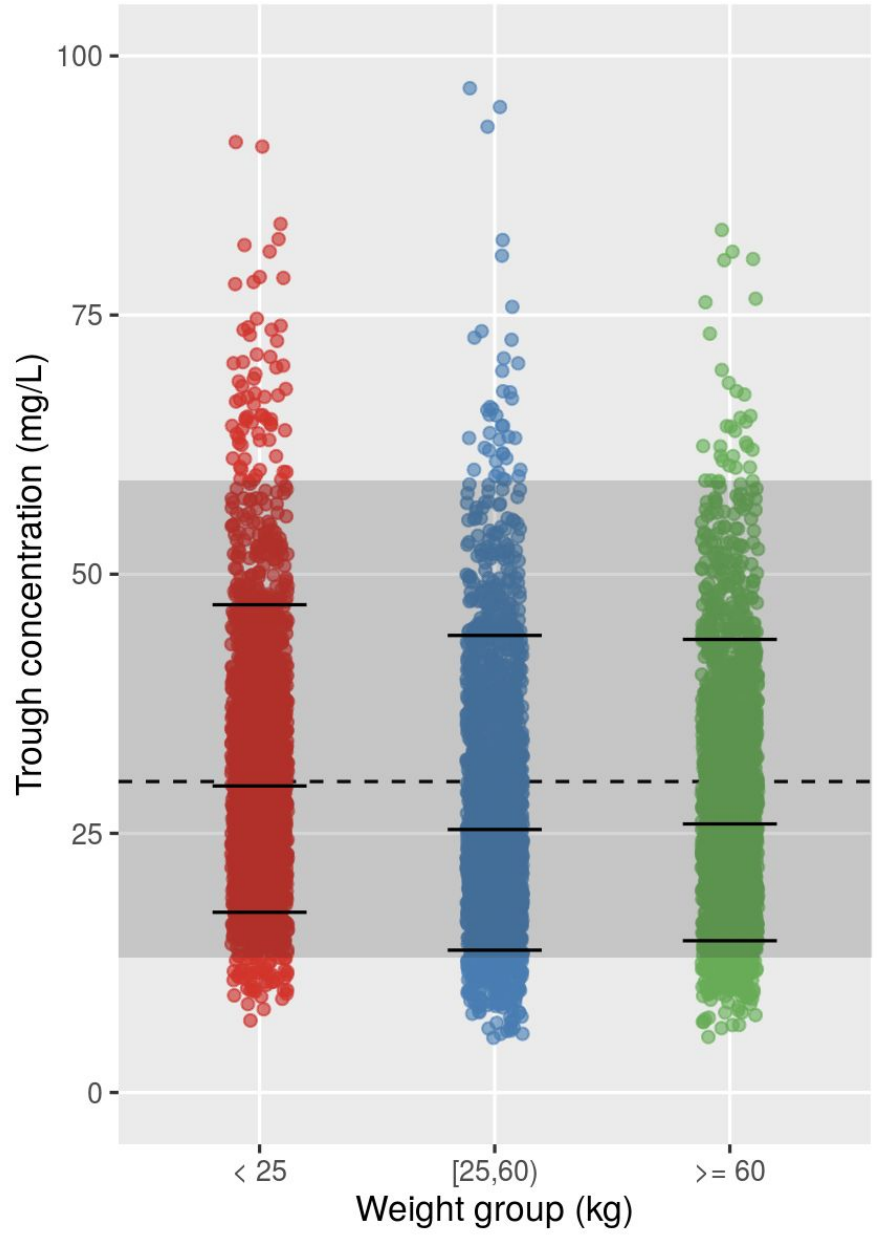

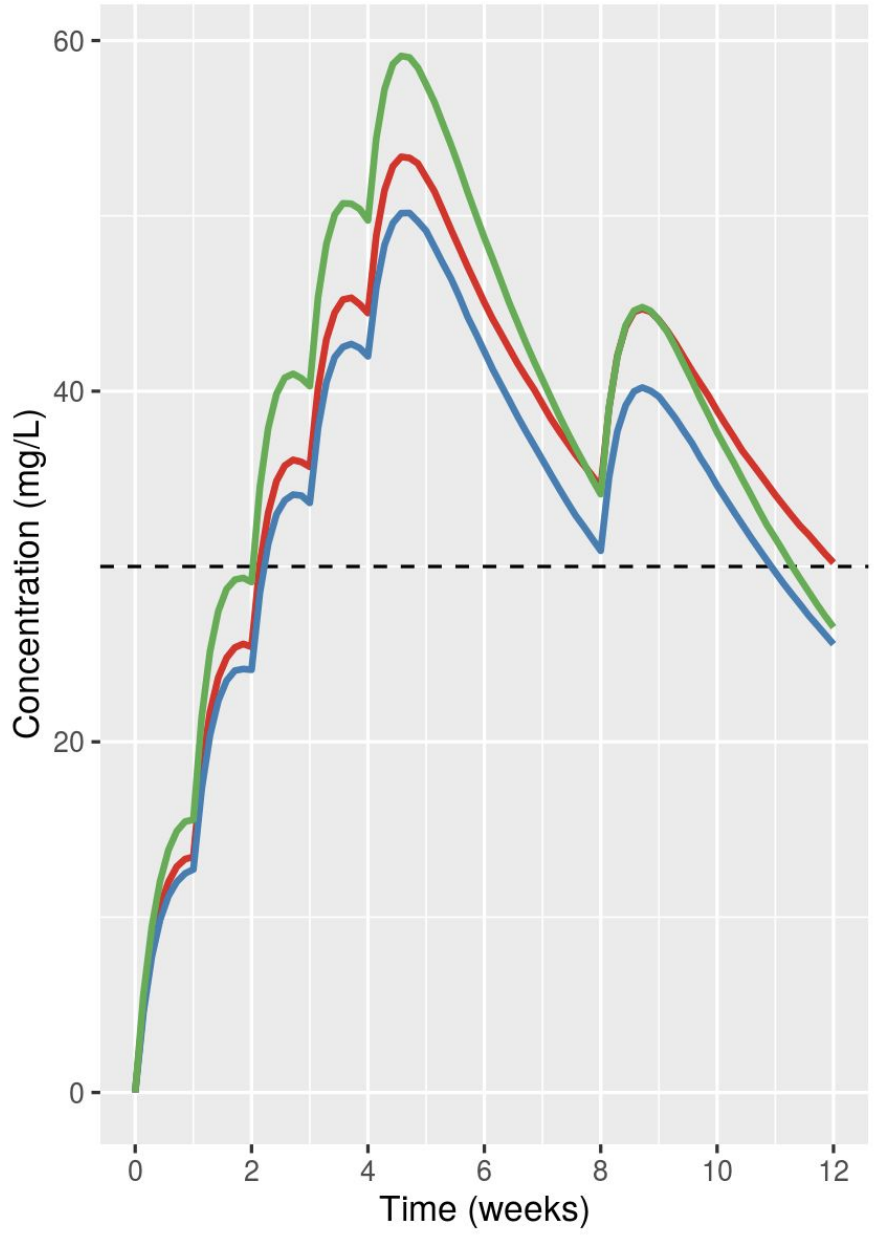

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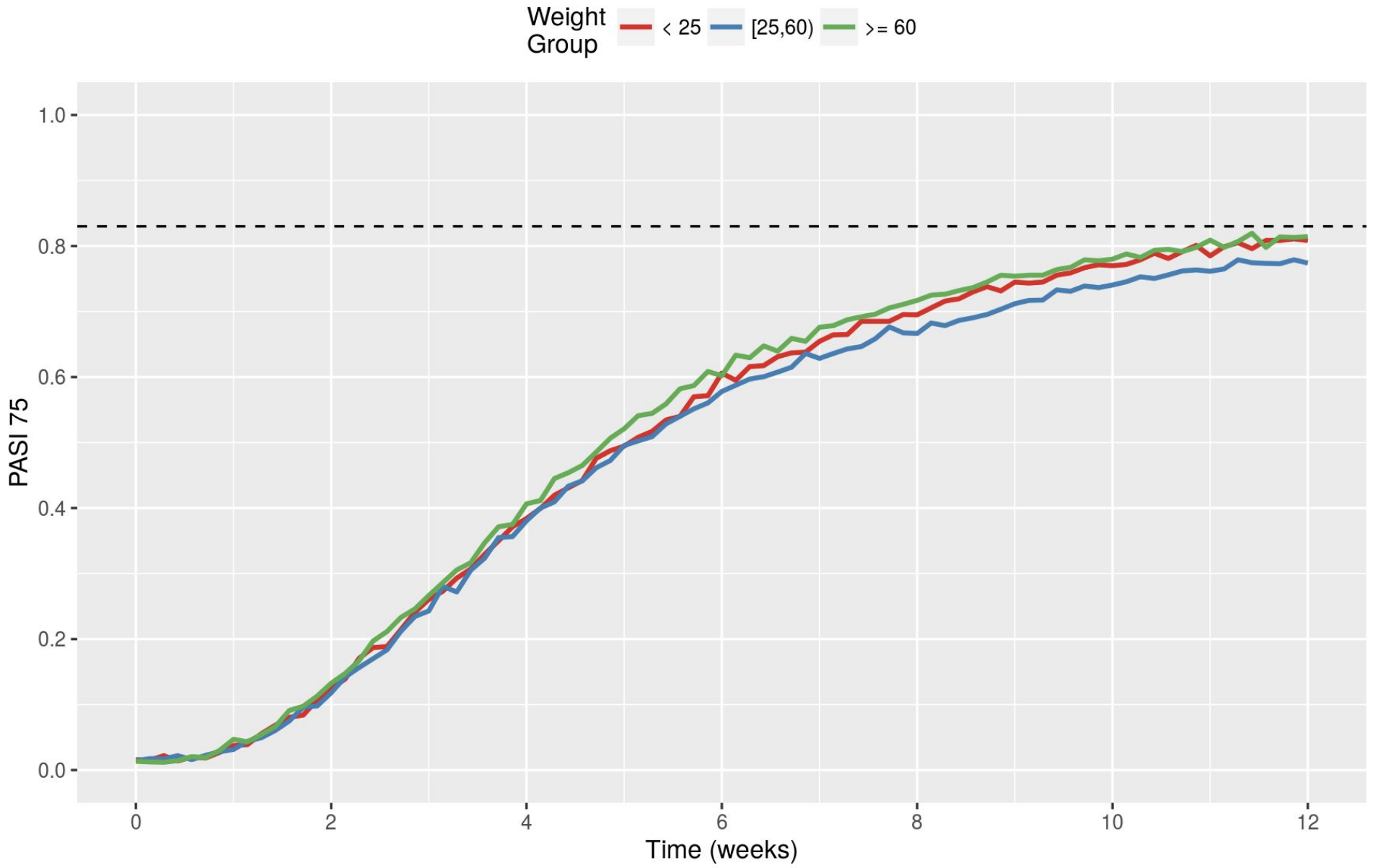

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