# Leveraging multiple R tools to make effective pediatric dosing decisions

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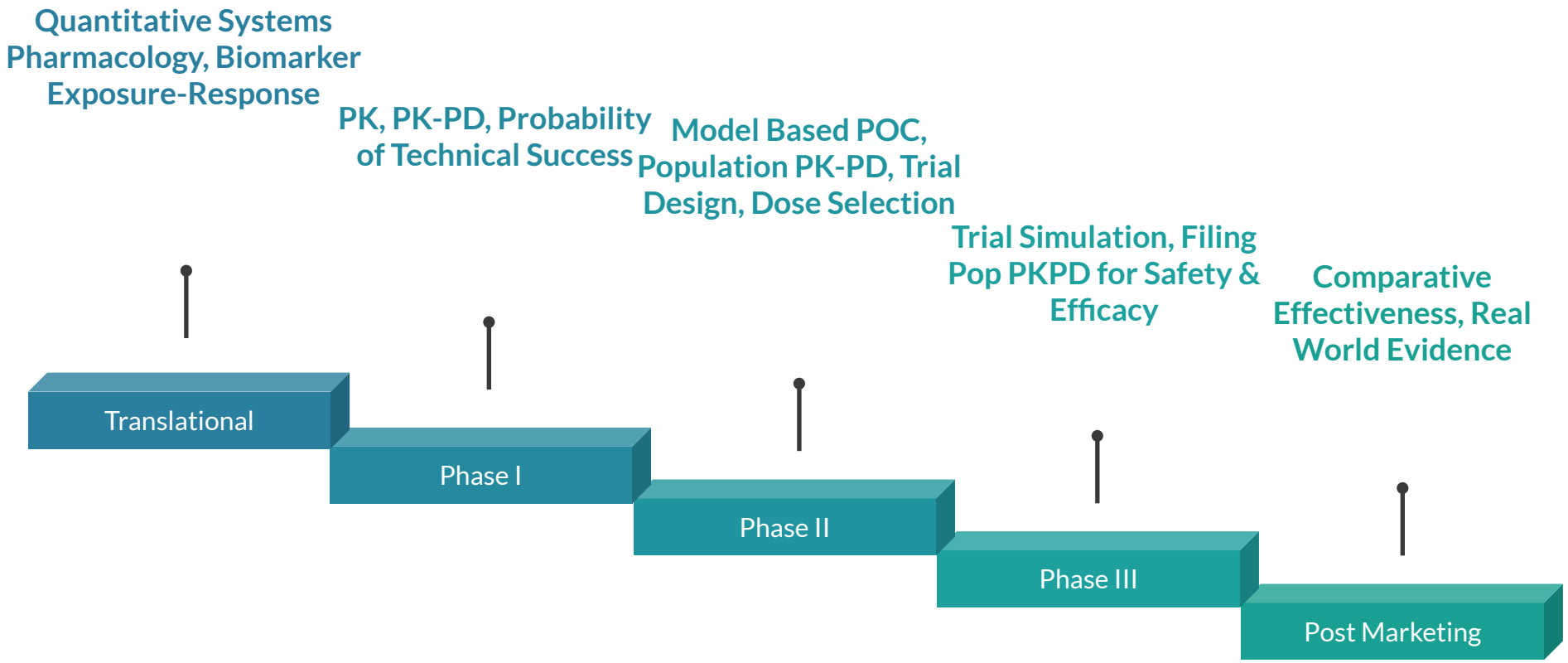
# Thanks to:

Marc Gastonguay, Ph.D
Kyle Baron, Ph.D

# Biomedical Decision Informatics



Bringing a quantitative approach to drug development




Off-The-Shelf Disease Area Platform Content: Disease Progression, Quantitative Systems Pharmacology, Competitor Model-Based Meta-Analysis, Trial Simulation Tools



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# Pediatric Drug Development Questions



Regulatory Expectations

Unique Therapeutic Setting

What dose?

What formulation?

What endpoints?

What age?

When?

How many?

Other considerations?

# A Typical Scenario - All Open Source



- Cosentyx® (Secukinumab)
- human IgG1 monoclonal antibody
- interleukin-17A antagonist
- 150 or 300 mg injection approved in adults
  - moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy
  - psoriatic arthritis
  - ankylosing spondylitis
- **Potential treatment in pediatric population**

https://metrumrg.shinyapps.io/mrgsolve-demo-acop7/

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Model Inputs

Pediatric dose (mg)

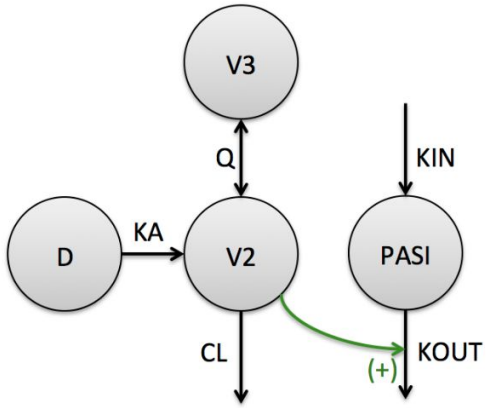
Weight groups (kg)

Select n weights and n+1 doses

PROBLEM | PLAN | EXPOSURE | OUTCOME

**secukinumab (COSENTYX®)**

- 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**

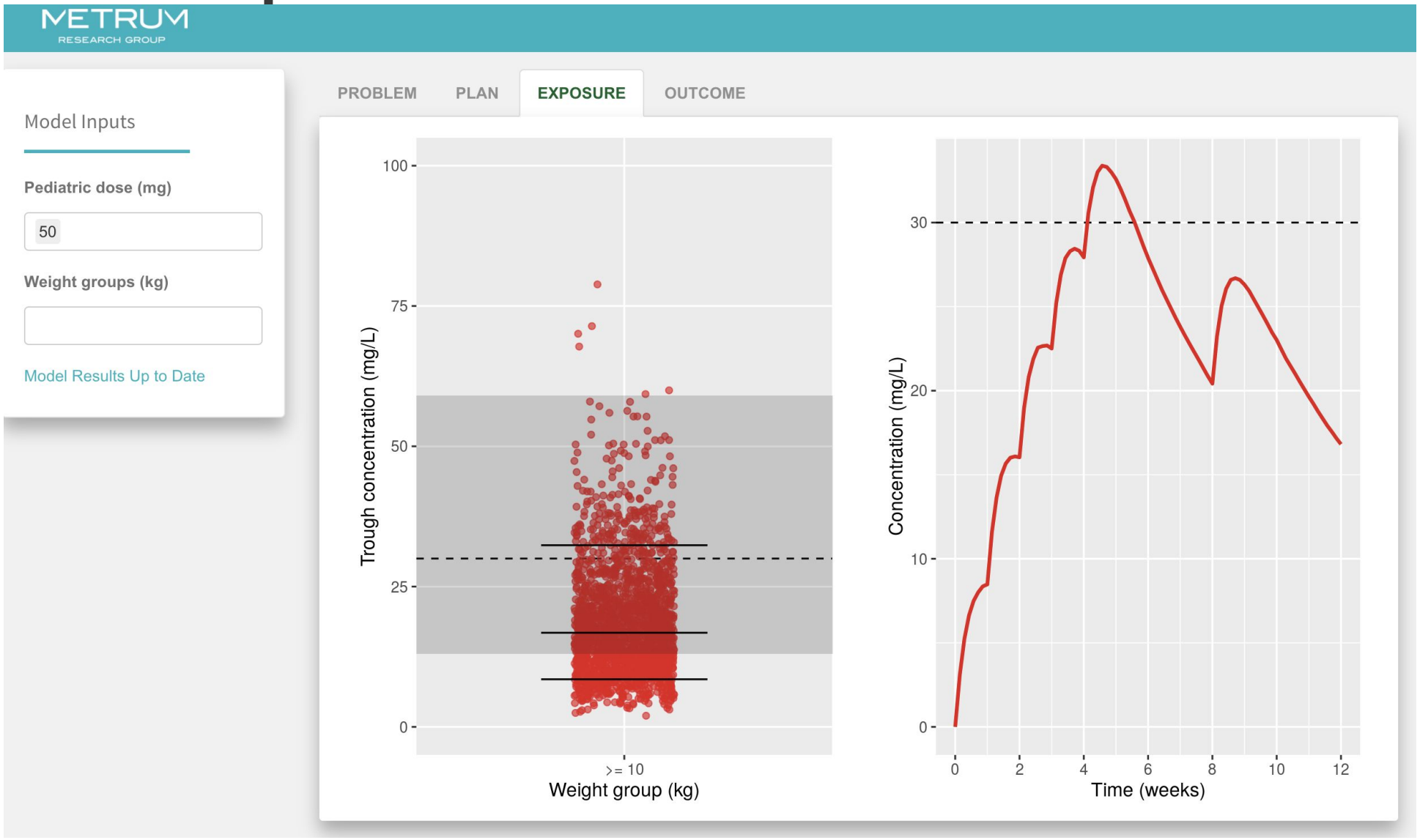
- What dose is appropriate in pediatric population?
- Should different weight groups get different doses?
  - How to compose weight groups?
  - What dose to give each group ?
- How might we conduct therapeutic drug monitoring?

**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

# Simulation: Exposure





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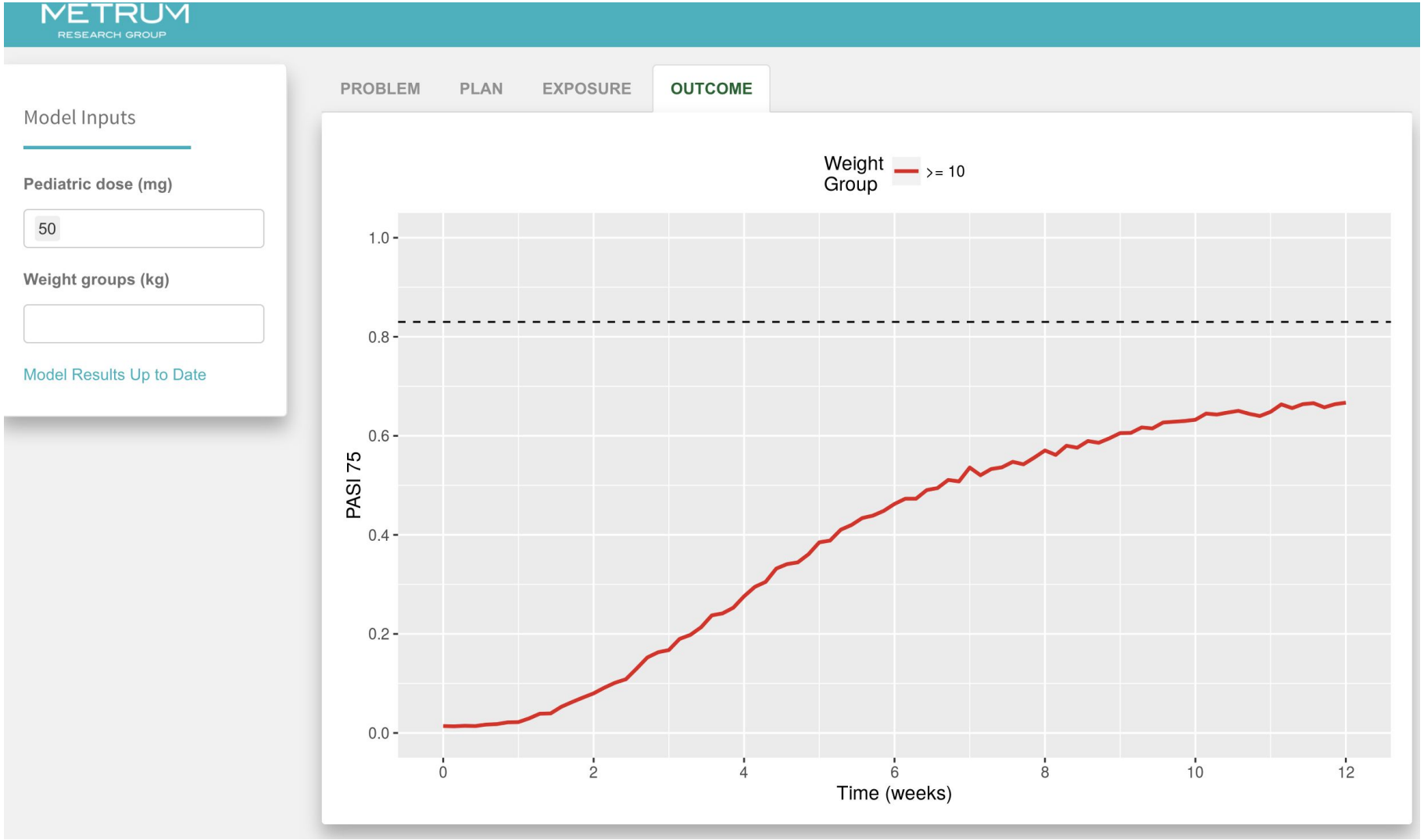
# Simulation: Outcome





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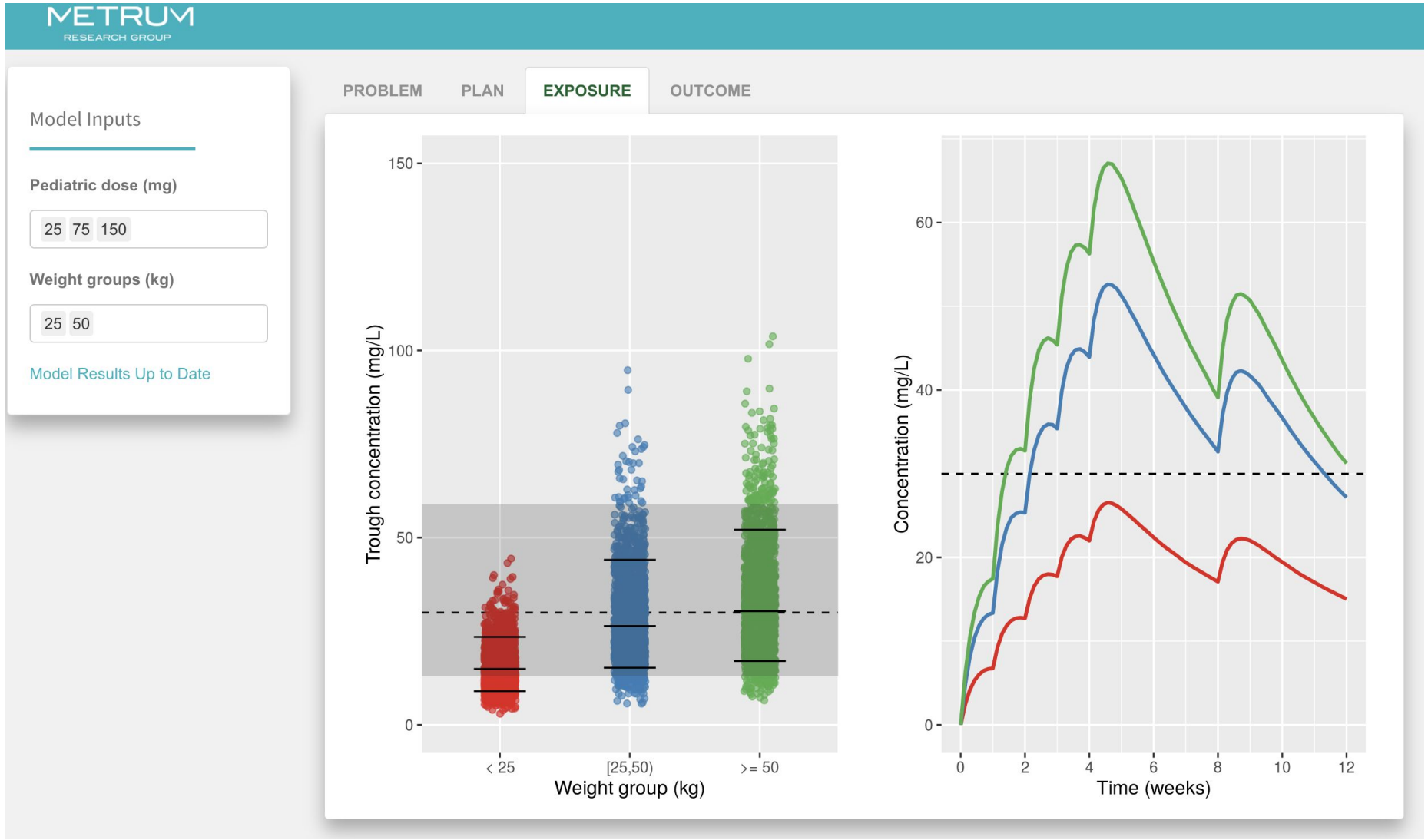
# Simulation: Exposure





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# Simulation: Outcome






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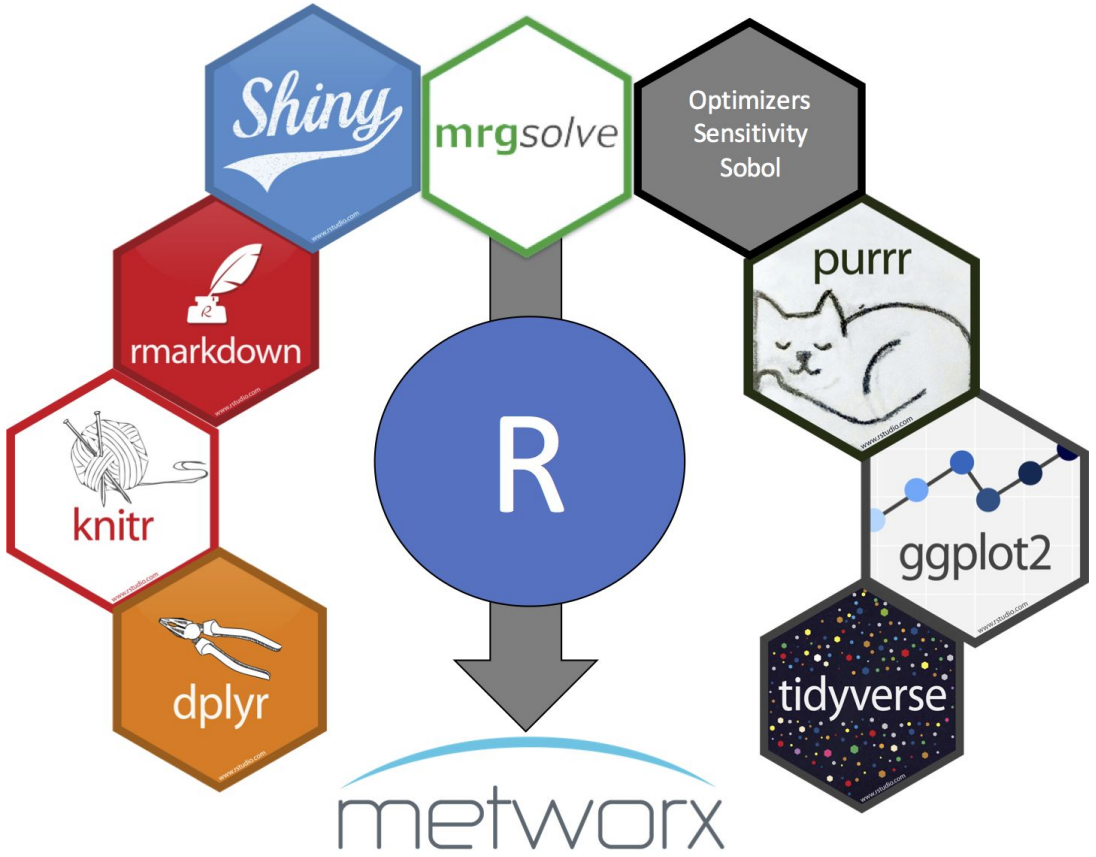
- Integration of tools
- Interactive simulation for decision makers
- Support for regulatory interactions
- Exploration of pediatric dosing rules



# References

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  - https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
- **Pediatric Investigation Plan (EMA)**
  - https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines/paediatric-investigation-plans
- **Shiny app**
  - https://metrumrg.shinyapps.io/mrgsolve-demo-acop7/
- **mrgsolve**
  - https://mrgsolve.github.io/
- Lee et.al., Effect of Body Weight on Risk-Benefit and Dosing Regimen Recommendation of Secukinumab for the Treatment of Moderate to Severe Plaque Psoriasis, *Clin. Pharm & Ther* (2019)

# THANK YOU!