Simulation Case Studies

Michael Heathman and Kyle Baron

October 25, 2019

METRUM
RESEARCH GROUP

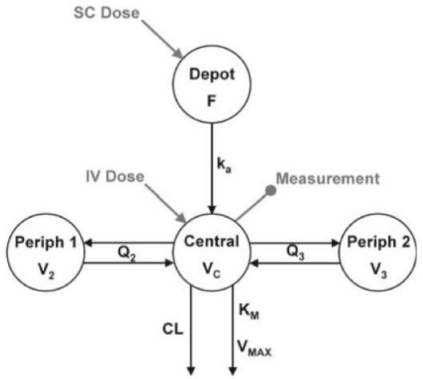
Fictional Fc-Osteoprotegrin Clinical Program

- Fc-Osteoprotegrin (OPG) is a genetically engineered fusion molecule, comprising an Fc-fragment and osteoprotegrin, currently in early Phase 1 development for the treatment of osteoporosis in postmenopausal women.
- OPG inhibits osteoclast activity by preventing the receptor activator of NF-kappa B ligand (RANKL) from binding to RANK on the surface of precursor and mature osteoclasts, slowing bone resorption and contributing to the natural maintenance of bone homeostasis.
- The primary efficacy measure for OPG is urinary N-telopeptide/creatinine ratio (NTX), a marker of bone resorption.
- It is believed that a sustained 40% reduction in NTX will correlate to a clinically significant reduction in fracture risk
- A very large (and expensive) Phase 3 program will be needed to test this hypothesis, due to the low incidence rate of fractures, so it's important to get the dose right.

METRUM
RESEARCH GROUP

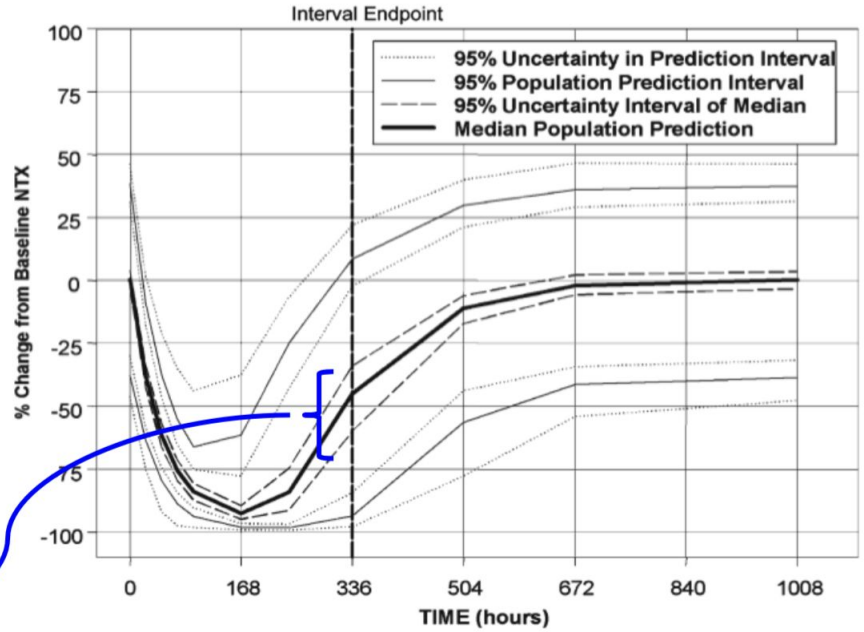
PK-PD Model of Fc-Osteoprotegrin

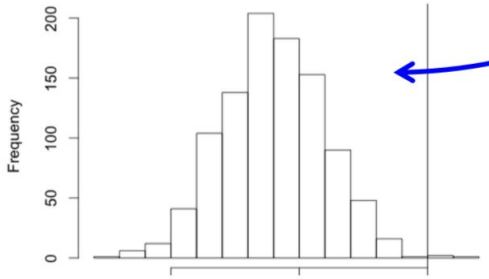
Fig. 1 Final compartmental model for Fc-OPG pharmacokinetics. V_C is the central compartment volume of distribution, V_2 and V_3 are the peripheral compartments' volumes, Q_p is the intercompartmental clearance between the central compartment and compartment p, CL is the linear clearance from serum, and V_{max} and K_M describe Michaelis–Menten elimination. Subcutaneously injected compound had a first-order absorption rate of k_a and a bioavailability of F. See text for more details



$$\frac{dNTX(t)}{dt} = k_{syn}\left(1 - \frac{I_{MAX}C_{OPG}(t)}{IC_{50} + C_{OPG}(t)}\right) - k_{deg}NTX(t)$$

population variability and parameter uncertainty





Typical change from baseline NTx at 336 hours

Fig. 7 Simulation of 200 replicate trials, each with 200 subjects, based on a single SC dose of 3 mg/kg, reflecting cohort 4 dosing in the original data set (body mass was assumed to be 70 kg for all subjects). The thick solid line represents the median value of all median NTX percent changes from baseline (across the 200 simulated trials; one median value is obtained from each simulated trial). The dashed lines delimit the 95% uncertainty interval for the population median value. The thin solid lines show the median values of all 95% population variability prediction intervals (across the 200 simulated trials). The dotted lines show the 95% uncertainty interval in the population 95% prediction intervals. The vertical dashed line intersects the computed profiles at 2 weeks after drug administration, and it helps to gauge visually how effective a biweekly dosing regimen might be. See text for further details

Zierhut et al. *J Pharmacokinet Pharmacodyn. 2008 Aug;35(4):379-99. Epub 2008 Jul 17.*

METRUM RESEARCH GROUP

Files for Case Studies

Models/

- opg_pk.mod : mrgsolve implementation of OPG PK model
- opg_pkpd.mod : mrgsolve implementation of OPG PK/PD model for NTX
- opg_fracture.mod : mrgsolve implementation of OPG fracture model

Data/

- demographics.csv : database of ages and weights for postmenopausal women
- SAD_params.csv : Table of individual parameter estimates from Cohort 1 of SAD study
- post_POC.csv : Bayesian posteriors from POC study
- post.csv : Bayesian posteriors from pooled Phase 2 analysis

Scripts/

- Exercise_1.R : Deterministic Simulation
- Exercise_2.R : Simulation with Variability
- Exercise_3.R : Simulation with Uncertainty
- Exercise_4.R : Probabilistic Simulation
- Exercise_5.R : Population Simulation

METRUM
RESEARCH GROUP

Exercise 1: Deterministic Simulation

The first cohort of the Phase 1 single ascending dose (SAD) study has completed, with 8 patients receiving 0.1 mg/kg of OPG. Using this data, you've developed a PK model and have individual parameter estimates for all the patients in this cohort.

The team is interested in knowing what these patient's exposures would be if they received a single dose of 1 mg/kg OPG in the next cohort. Due to tox concerns they want to be sure that maximum concentrations remain below 5,000 ng/mL.

Question:

- What would these patient's exposures ($AUC_{0\text{-}168}$, Cmax) be if they received a single dose of 1 mg/kg OPG in the next cohort?

Extra Credit:

- What is the maximum single dose of OPG that could be administered to these patients without any of their concentrations exceeding 5,000 ng/mL?

METRUM
RESEARCH GROUP

Simulation Map for Deterministic Simulation

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)			
Population/Trial (p)			
Individual (i)	CL_i, V_i, … → Cp(t) $Weight_i$ → Dose Amount	1 mg/kg single dose	8
Occasion (k)			1
Observation (t)	Cp(t)	0:168 hours	169

METRUM RESEARCH GROUP

Exercise 1: Deterministic Simulation

Files

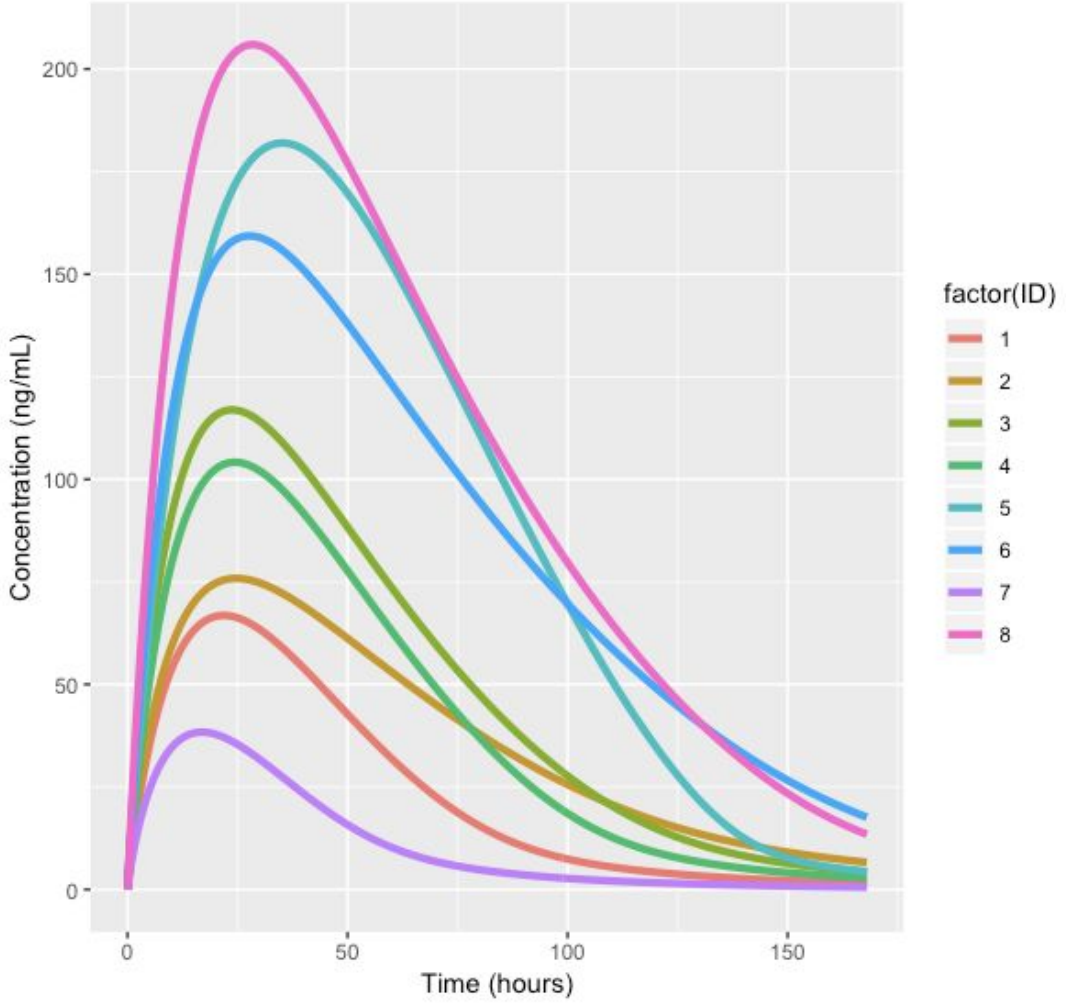
- opg_pk.mod — mrgsolve model for OPG PK
- SAD_params.csv — Individual parameter estimates and body weights for Cohort 1
- Exercise_1.R — R script to implement simulation

Implementation Notes

- What's the most efficient way of calculating AUC in your simulation code?
  Accumulation compartment to integrate concentration over time.
- Set fixed effects to individual parameter estimates.
- No uncertainty, no variability
  mod <- mod %>% zero_re() **#**sets OMEGA and SIGMA matrices to zero in mrgsolve.
- Body weight set to observed value for each patient for mg/kg dose calculation.
- **Make sure inclusion of body weight in data does not change individual parameter estimates.**

METRUM
RESEARCH GROUP

Exercise 1: Deterministic Simulation



Exposures following single dose of 1 mg/kg

ID	CMAX (ng/mL)	AUC (ng*hour/mL)
1	67.4	4008
2	76.5	6280
3	116	8296
4	104	7003
5	182	15060
6	160	14541
7	38.2	1844
8	206	17554

METRUM RESEARCH GROUP

Exercise 2: Simulation with Variability

The SAD and MAD studies have been completed and the PK model has been updated using this data. The team is planning the upcoming Phase 2 proof of concept (POC) study, which will use a once-weekly (QW) dosing regimen.

Preclinical experiments have suggested that the IC50 for OPG is around 10 ng/mL. The team would like to maintain exposure above the IC90 (90 ng/mL) throughout the dosing interval, to maintain at least 90% inhibition. At the same time they would like to keep maximum concentrations below the 5,000 ng/mL tox limit.

Question:

1. What dose is required to achieve trough concentrations above 90 ng/mL in 80% of patients, after weekly dosing for 4 weeks?

Extra Credit:

2. What is the maximum weekly dose that can be administered while maintaining maximum concentrations below 5000 ng/mL in 90% of patients?

METRUM
RESEARCH GROUP

Simulation Map for Simulation with Variability

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)			
Population/Trial (p)	CL_p **Ω** **Σ** Patient Database	1-12 mg/kg QW	12
Individual (i)	η_{CLi} → CL_i ← $Weight_i$		1000
Occasion (k)			1
Observation (t)	Cp(t) ← ε_t	0:168 hours	169

METRUM RESEARCH GROUP

Exercise 2: Simulation with Variability

Files

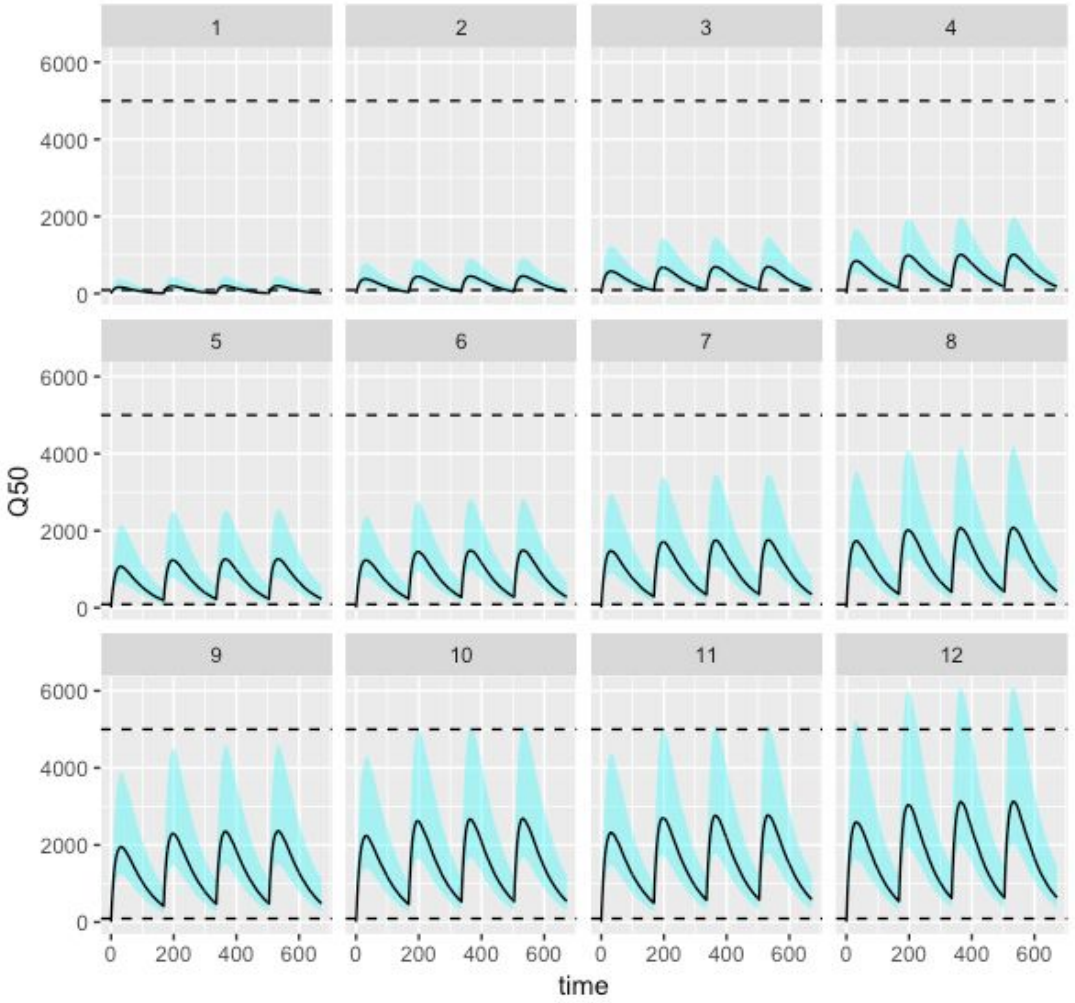
- opg_pk.mod — mrgsolve model for OPG PK
- demographics.csv — Database of ages and weights for postmenopausal women
- Exercise_2.R — R script to implement simulation

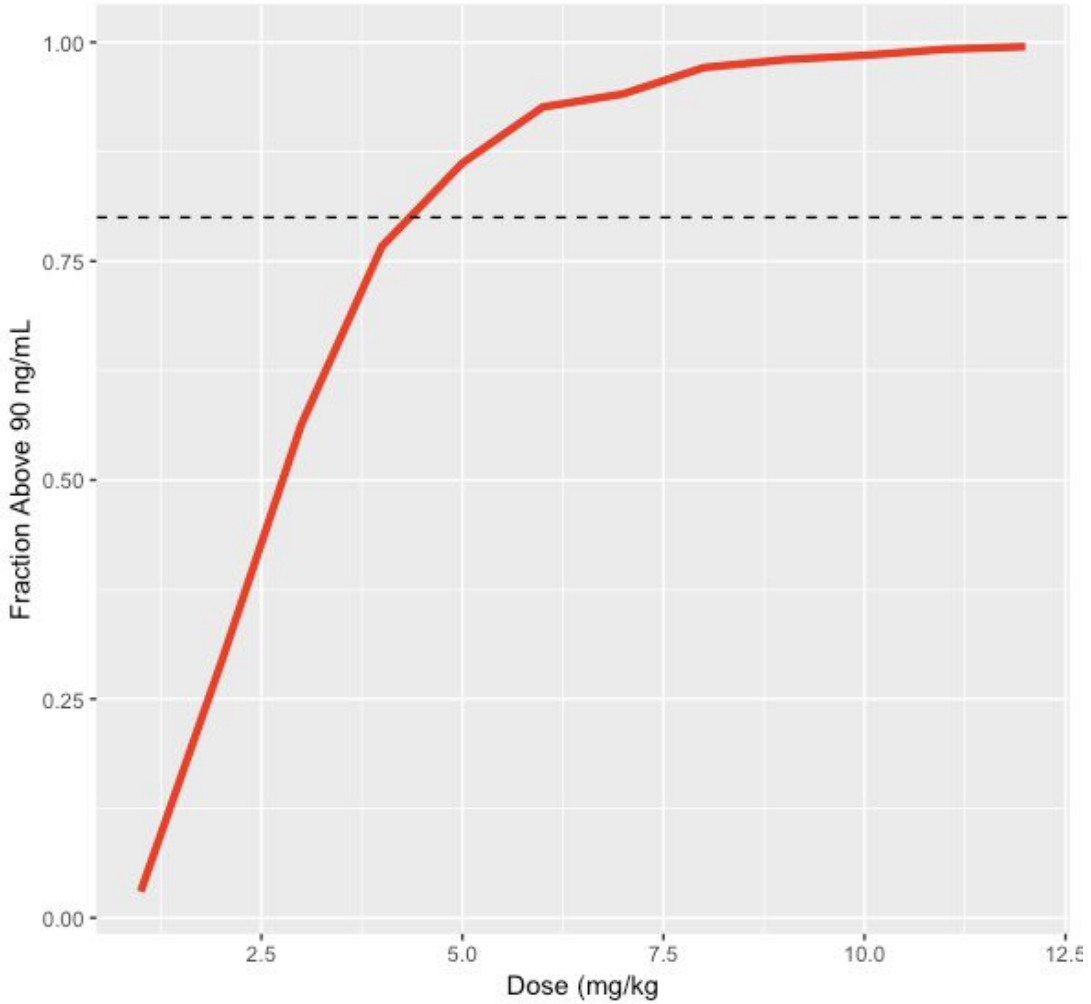
Implementation notes:

- Use database of patient weights to inform parameter values and set dose amounts.
- Use addl to implement additional doses, addl=3 provides a total of 4 doses.
- Remove residual error as we're interested in actual concentrations, not what is observed.
  mod <- mod %>% zero_re(sigma)

METRUM
RESEARCH GROUP

Exercise 2: Simulation with Variability





METRUM
RESEARCH GROUP

Exercise 3: Simulation with Uncertainty

The POC study has been completed and you've developed an indirect response model to describe the effect of OPG on NTX reduction. Uncertainty in IC50 is high, due to the limited dose range in the POC study. A Bayesian analysis was conducted to understand uncertainty in IC50 and other model parameters.

The team is designing a Phase 2 dose ranging study and you'd like them to consider longer dosing intervals, as turnover of NTX appears to be slow and NTX suppression was sustained following the last dose in the POC study. You have a team meeting in 2 hours ...

Question:

- What is the probability that a 5 mg/kg dose would achieve the target of 40% mean reduction in NTX at trough, if administered every 2 weeks for 3 months?

Extra Credit:

- What dose would provide a 90% probability of achieving this target with Q2W dosing? With Q3W dosing?

METRUM
RESEARCH GROUP

Simulation Map for Simulation with Uncertainty

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)	Posteriors		
Population/Trial (p)	CL_p $IC50_p$ Patient Database → Mean WT	5 mg/kg Q2W	1000
Individual (i)			1
Occasion (k)			1
Observation (t)	NTX(t)	336 hours	1

METRUM RESEARCH GROUP

Exercise 3: Simulation with Uncertainty

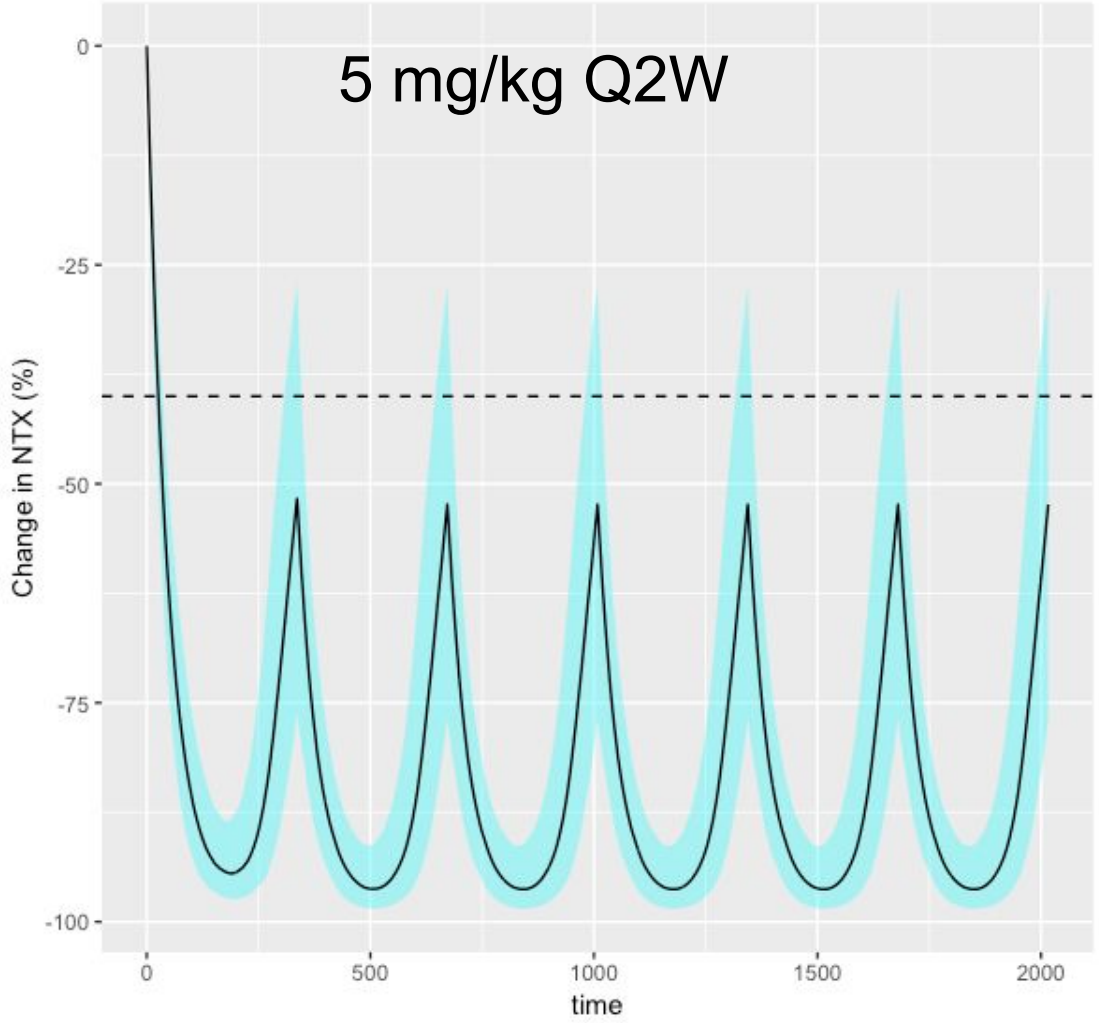
Files

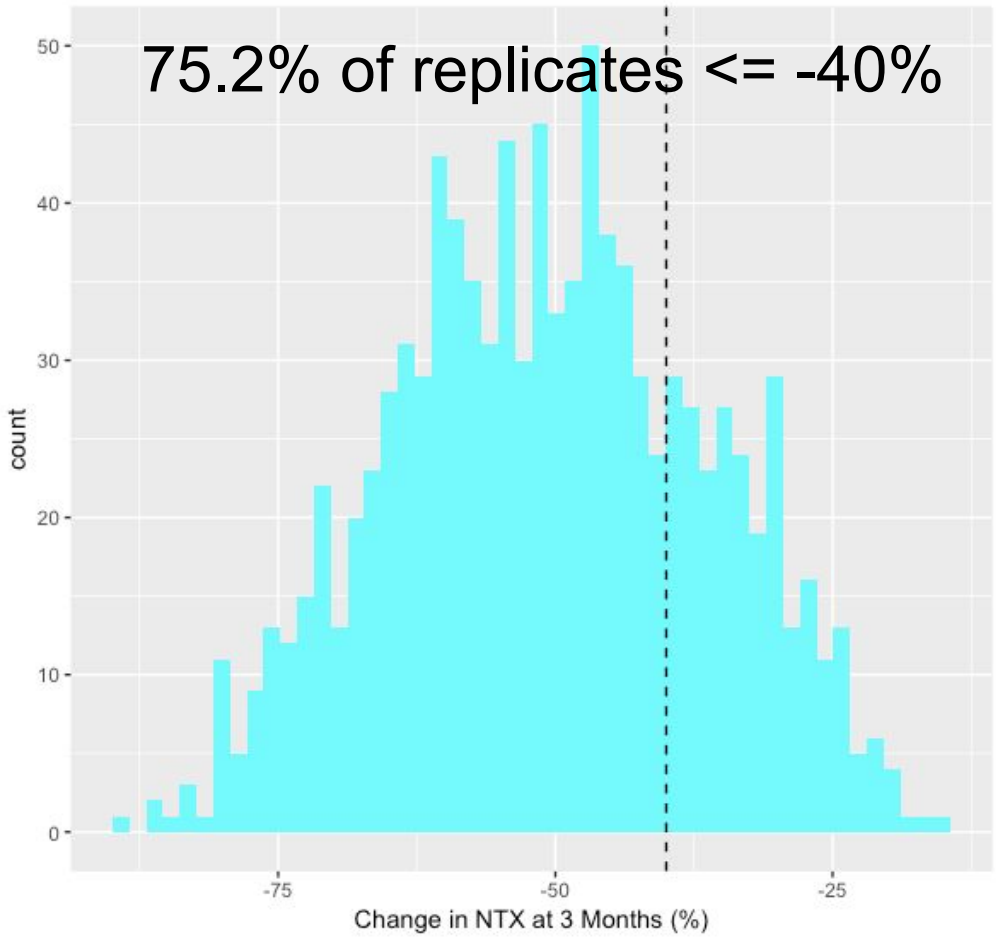
- opg_pkpd.mod — mrgsolve model for OPG indirect response
- post_POC.csv — Bayesian posteriors from POC analysis
- demographics.csv — Database of ages and weights for postmenopausal women
- Exercise_3.R — Script to implement simulation

Implementation:

- Using typical response as a surrogate for the mean.
- Include uncertainty, sampled from Bayesian posteriors, in order to make probabilistic statement.
- Calculate mean weight for population from patient database (each replicate is a population).
- Remove all variability using zero_re().
- Percent change from baseline coded into mrgsolve model.

Exercise 3: Simulation with Uncertainty





METRUM
RESEARCH GROUP

Exercise 4: Probabilistic Simulation

The dose ranging study has been completed and your PK/PD model has been updated with this new data. Uncertainty in your model parameters is much lower and you've run another Bayesian analysis to quantify it.

The team is now planning for the pivotal Phase 3 study. Marketing is pushing for flat dosing, rather than weight-based, to simplify dose administration and reduce wastage. The team wants to know if this is viable.

Question:

- If a 400 mg Q2W dosing regimen is taken into Phase 3, what is the probability that an individual patient will achieve a 40% reduction in NTX at steady-state trough?

Extra Credit:

- If two flat doses are taken into Phase 3, one for patients < 70 kg and one for patients >= 70 kg, what doses are required for patients to have a 80% probability of achieving the target?

METRUM
RESEARCH GROUP

Simulation Map for Probabilistic Simulation

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)	Posteriors		
Population/Trial (p)	CL_p $IC50_p$ Ω_p Σ_p Patient Database	400 mg Q2W	1000
Individual (i)	η_i $Weight_i$ CL_i $IC50_i$		1
Occasion (k)			1
Observation (t)	NTX(t) ε_{ij}	336 hours	1

METRUM RESEARCH GROUP

Exercise 4: Probabilistic Simulation

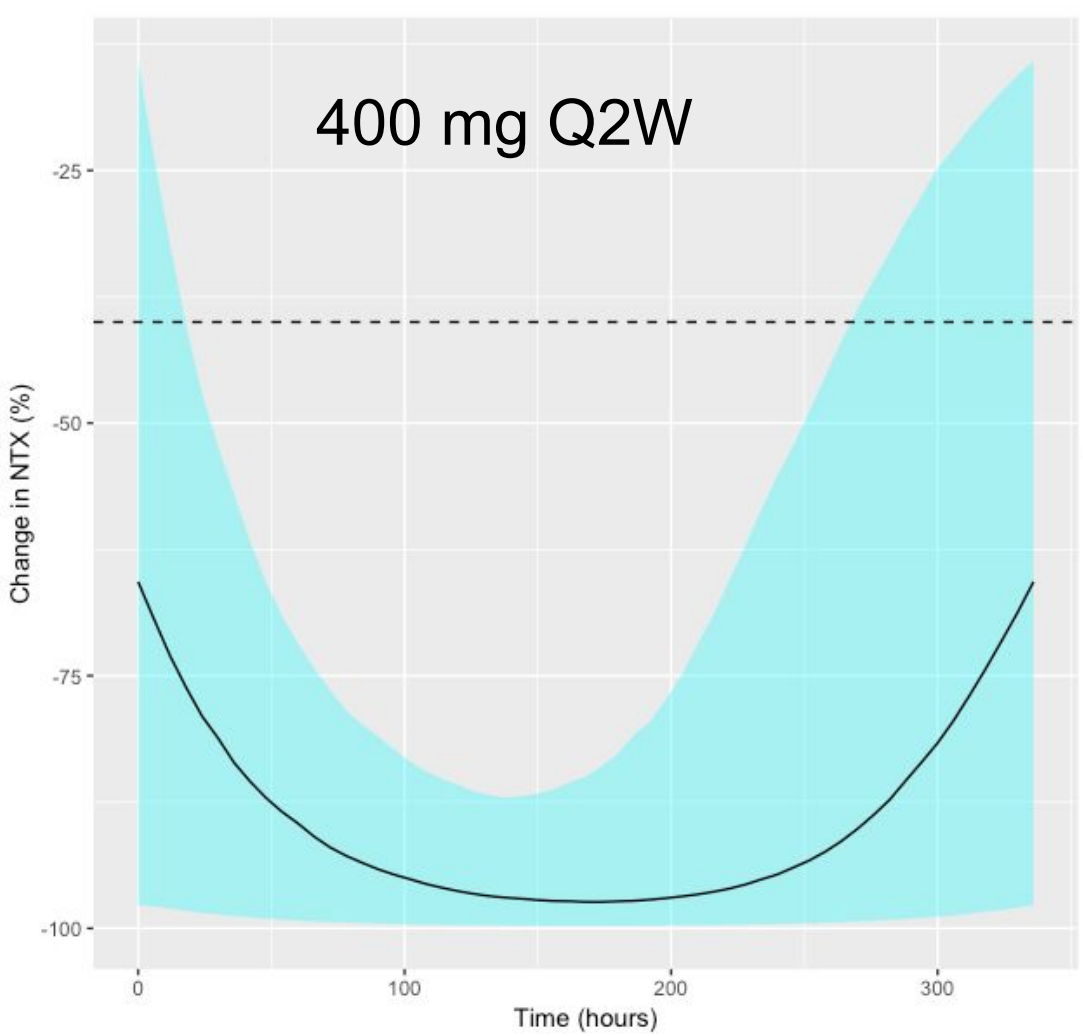
Files

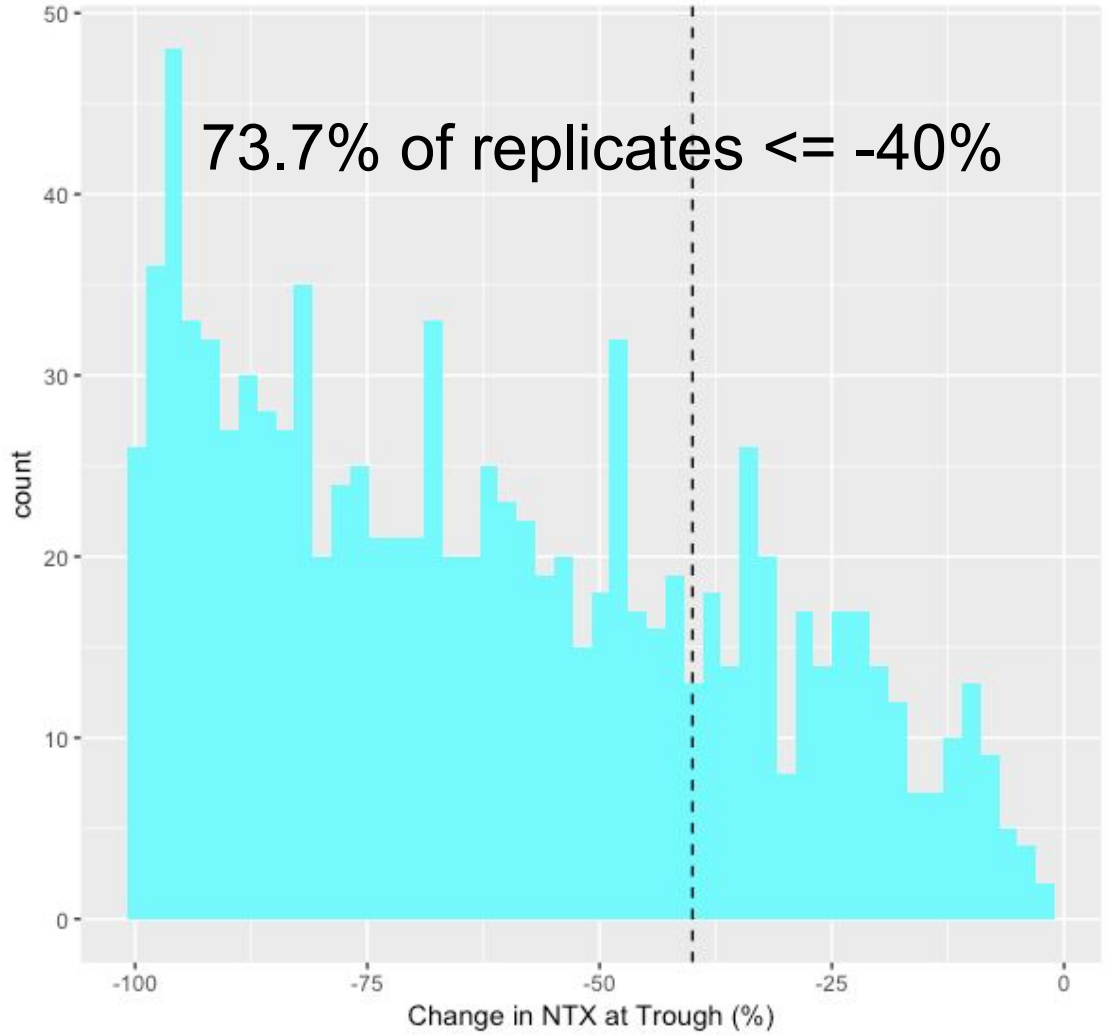
• opg_pkpd.mod	mrgsolve model for OPG indirect response
• post.csv	Bayesian posteriors from Phase 2
• demographics.csv	Database of ages and weights for postmenopausal women
• Exercise_4.R	Script to implement simulation

Implementation:

- Include uncertainty in order to make probabilistic statement, sampled from Bayesian posteriors.
- Sample patient weights from database.
- Remove residual error , since we're interested in patient's actual response, not what's observed. zero_re(sigma)
- Use ss=1 to generate steady-state predictions.

Exercise 4: Probabilistic Simulation





METRUM
RESEARCH GROUP

Exercise 5: Population Simulation

A competitor with a similar mechanism of action has just completed their Phase 3 study. The competitor's study demonstrated a mean reduction in NTX of 53% at steady-state and a 4.6% reduction in vertebral fracture risk relative to placebo. They've submitted an abstract for the ACR annual meeting with a logistic regression model for the effect of NTX reduction on fracture risk.

The team wants to know how likely it is that OPG can match the competitor's results. Your Phase 3 design calls for 1200 patients to be enrolled in a parallel study, randomized 1:1 to either placebo or 400 mg Q2W of OPG.

Question:

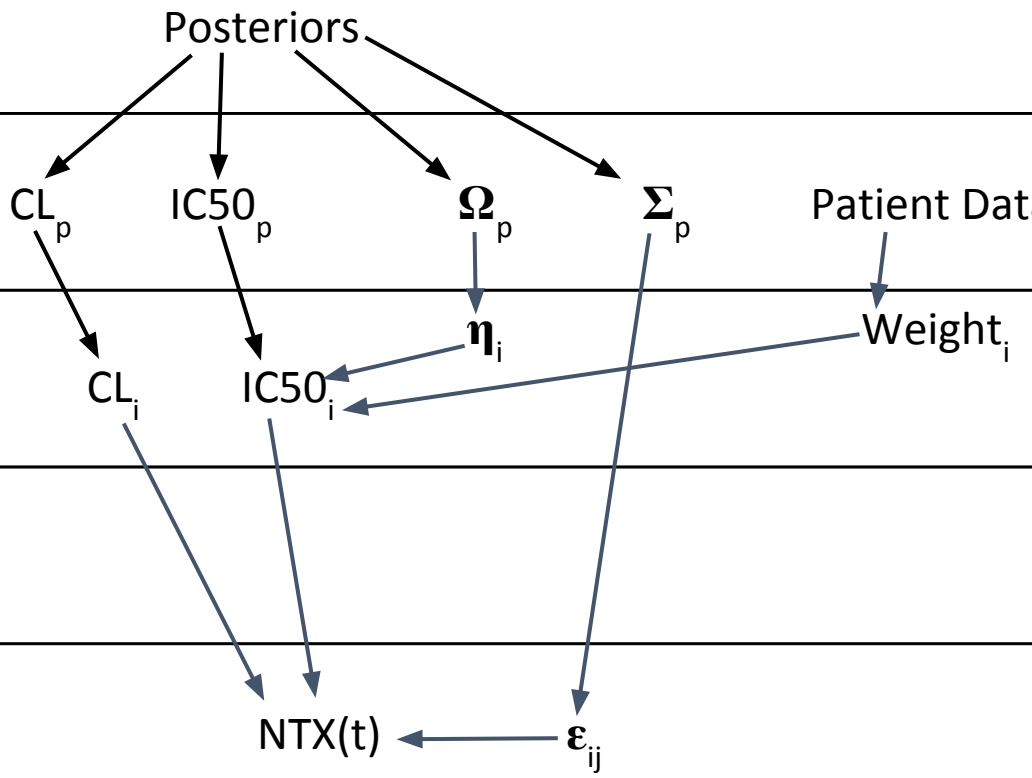
- What is the probability that at least a 53% mean reduction in NTX would be observed at steady-state in the OPG-treated study arm?

Extra Credit

- Using your competitor's fracture model, what is the probability that fracture risk will be reduced by 4.6% in the OPG-treated arm relative to placebo?

Simulation Map for Population Simulation

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)	Posteriors		
Population/Trial (p)	CL_p $IC50_p$ Ω_p Σ_p Patient Database	400 mg Q2W	1000
Individual (i)	η_i $Weight_i$ CL_i $IC50_i$		600
Occasion (k)			1
Observation (t)	NTX(t) ε_{ij}	336 hours	1



METRUM RESEARCH GROUP

Exercise 5: Population Simulation

Files

• opg_pkpd.mod	mrgsolve model for OPG indirect response
• opg_fracture.mod	mrgsolve model for fracture rate
• post.csv	Bayesian posteriors from Phase 2
• demographics.csv	Database of ages and weights for postmenopausal women.
• Exercise_5.R	Script to implement simulation

Implementation Notes

- Include uncertainty in order to make probabilistic statement.
- Include residual error, since we're looking for the observed mean.

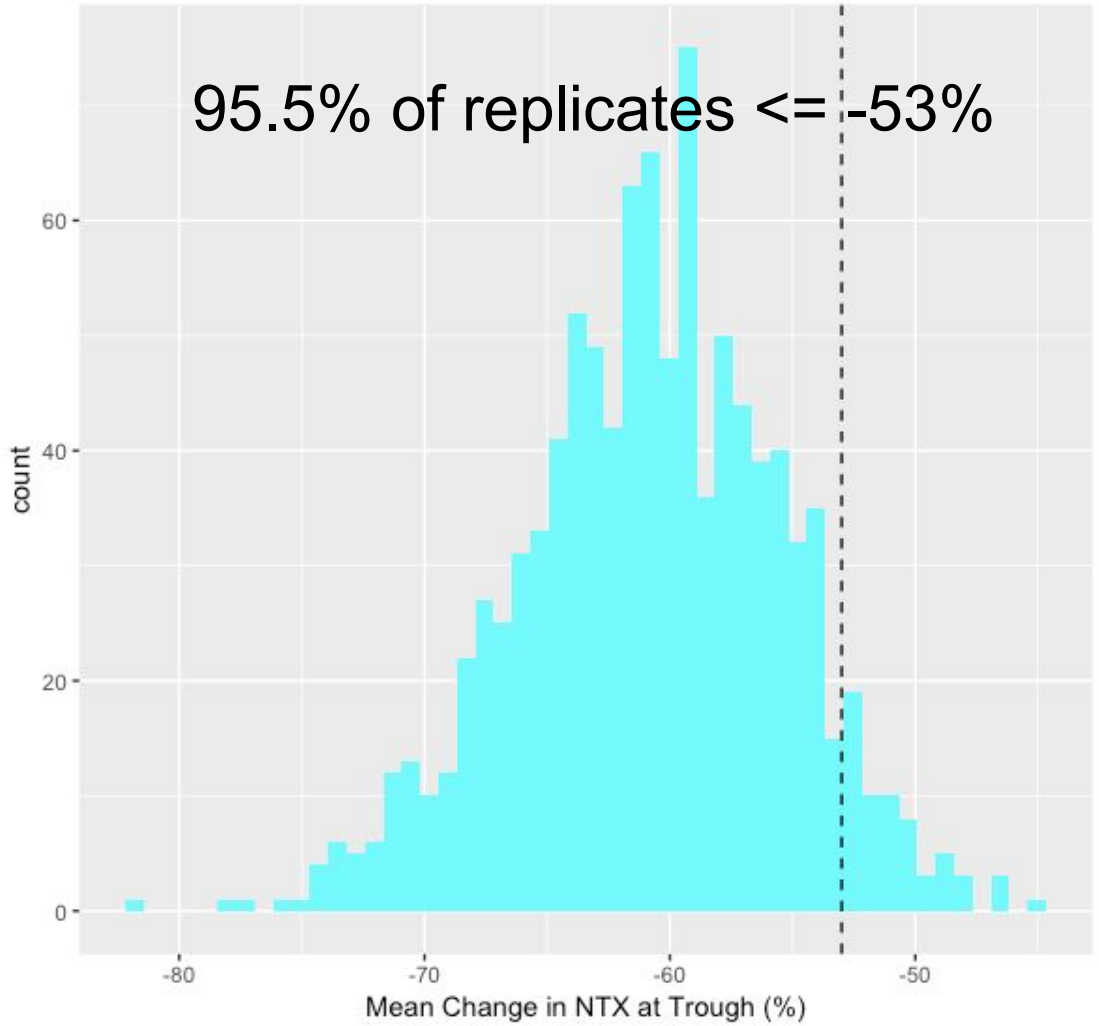
Logistic regression model for vertebral fracture risk in 3 year study:

Fracture Risk = $e^{logit}/(1+e^{logit})$

logit = -2.57 + 0.0164*(AGE-55) - 0.00975*(WT-70) + 0.0215*PCFB

METRUM RESEARCH GROUP

Exercise 5: Population Simulation



METRUM
RESEARCH GROUP

Exercise 6: Sensitivity Analysis

How robust are your predictions to uncertainty in your model parameters?

What information would be most beneficial in improving your predictions?

Implementation Notes

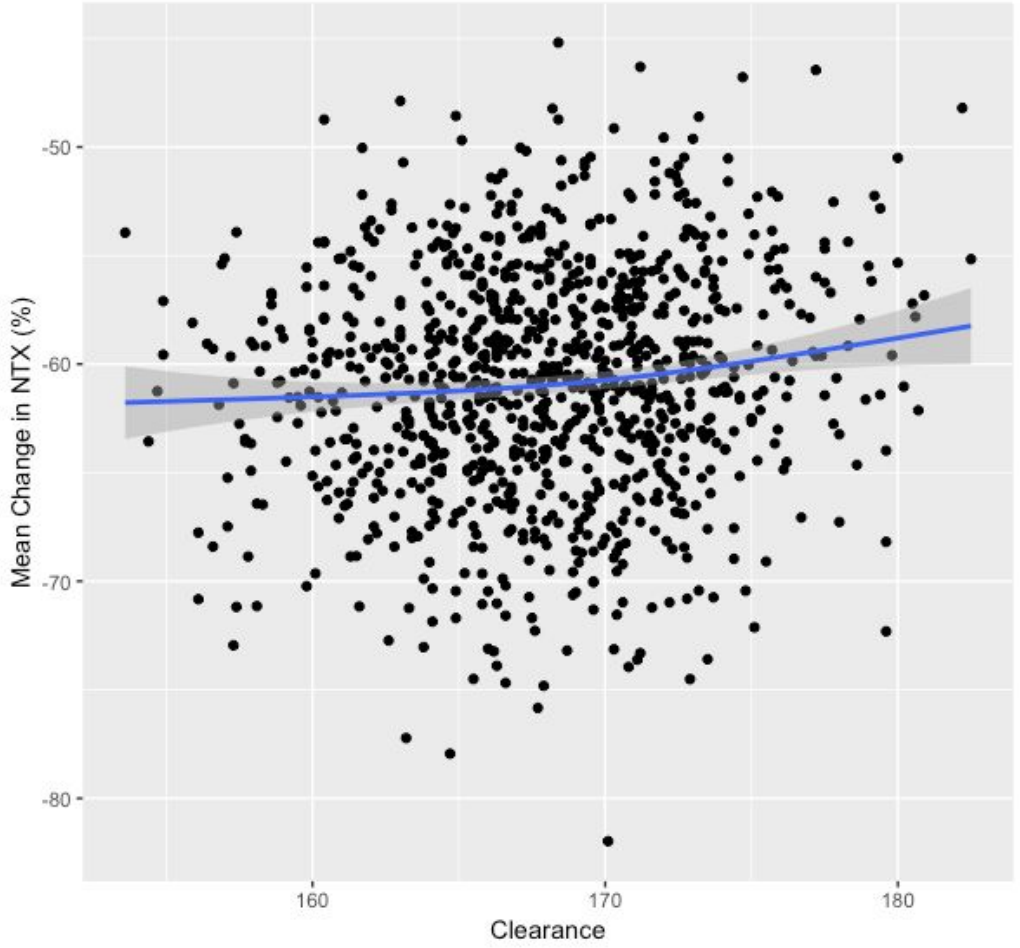
- Using the output from the population simulation, merge the mean predictions with the posteriors by replicate number.
- Plot parameter values vs the mean predictions to look for trends.

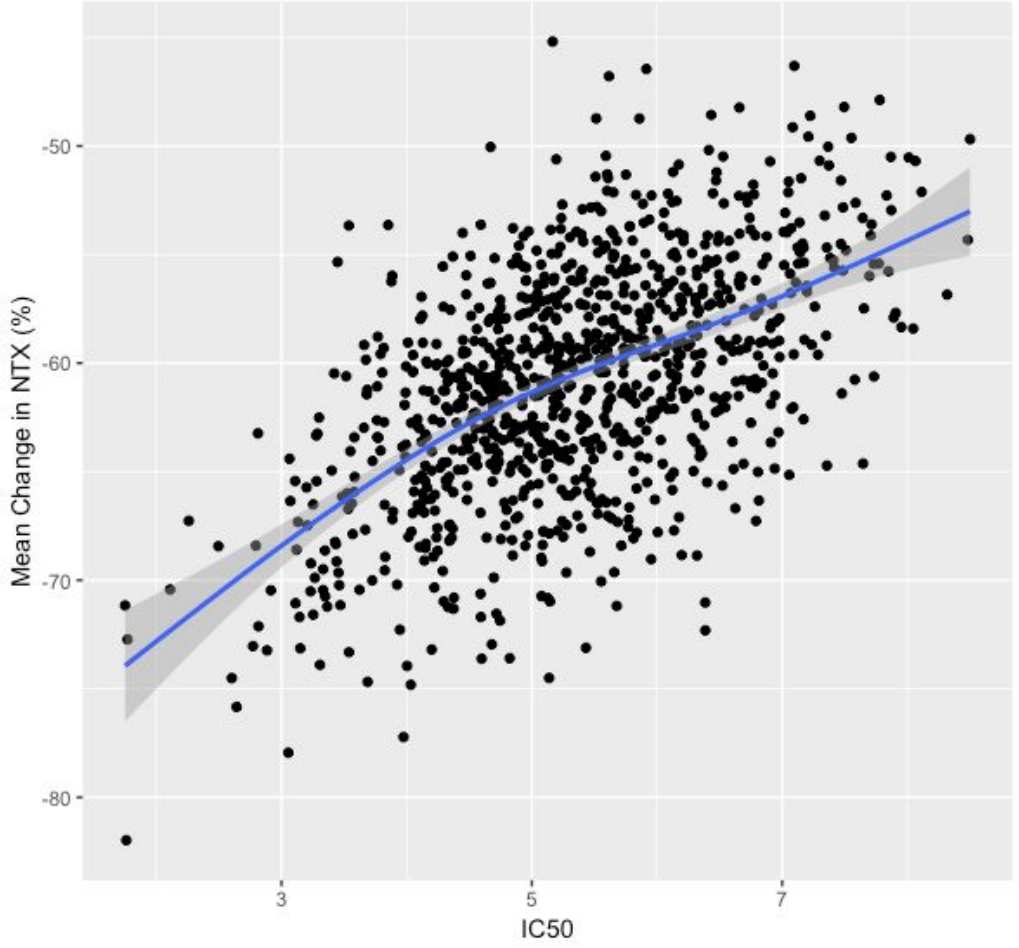
Code included in Exercise_5.R

METRUM
RESEARCH GROUP

Sensitivity Analysis

Improved understanding of IC50 would help improve prediction of mean response, while information about clearance would have very little impact.





METRUM
RESEARCH GROUP

the end

METRUM
RESEARCH GROUP