Simulation Concepts

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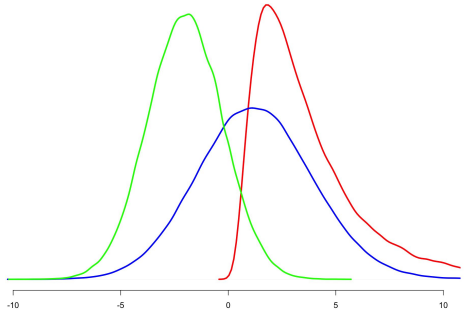
Outline

- **Basic Simulation Concepts**
- Construct Simulation Map
- Implement Simulation
- Sensitivity Analysis

Simulation Nomenclature

- **Fixed effects**: Population parameters that define the basic mathematical structure of the model.
- **Random effects**: Population parameters that quantify unexplained variability
  - Inter-individual variability: Unexplained variation in model parameters between patients
  - Inter-occasion variability: Unexplained variation in model parameters between occasions
  - Residual unexplained variability: Unexplained variation between observations within a patient
- **Parameter uncertainty**: How well the population parameters (fixed and random effects) are known or estimated.
- **Covariates**: Patient characteristics that influence model parameters. Describe sources of measurable variability across patients.
- **Replicate**: A single set of virtual responses created using simulation. Large numbers of replicates are required for stochastic simulations.

General Simulation Process



Parameter Uncertainty

Simulation Design

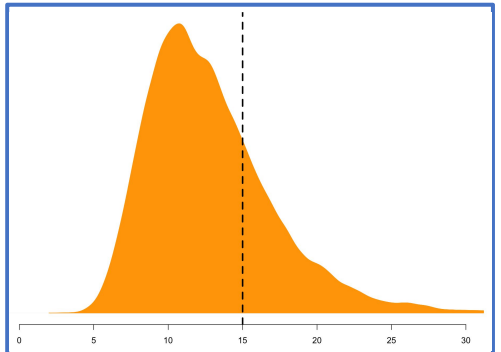
Treatment regimen
Study duration
Sampling schedule

Population Parameters

$\theta \quad \omega^2 \quad \sigma^2$

PK/PD Model

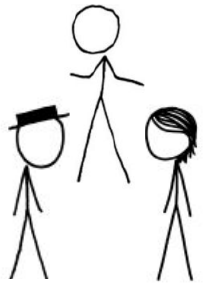
$$\frac{dA}{dt} = K_{IN} \cdot \left(1 + \frac{C_p * E_{max}}{C_p + EC_{50}}\right) - K_{OUT} \cdot A$$



Response distributions

Patient Characteristics

AGE	WT	BMI
27	68	23
48	85	34
33	78	29



Individual Parameters

KA, CL, V, E_0, E_{MAX}, EC_{50}, …

Probabilistic statements

A 150 mg QD dose has a 73% change of achieving a 1.2% reduction in HbA1c at 6 months.

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Types of Simulation

- Deterministic vs. Stochastic simulation
- Patient-Level vs Population-Level simulation
- Drug property vs Clinical Trial simulation

The incorporation of simulation components depend on the type of simulation conducted and the question to be answered:

- Parameter uncertainty
- Covariates
- Inter-individual / Inter-occasion Variability (IIV/IOV)
- Residual Unexplained Variability (RUV)

Deterministic vs. Stochastic Simulations

- **Deterministic (fixed effect) simulations**
  - Produce response for typical population or for specific individual(s)
  - Fixed Effects (THETAs) ➔ Typical response for population
  - Empirical Bayes Estimates ➔ Individual response for specific patients
- **Stochastic (Monte Carlo) simulations**
  - Produce the expected distribution of responses, given some sampling hierarchy and multiple simulation replicates.
  - Requires Monte Carlo sampling using a random number generator
  - Requires random variable sampling at one or multiple levels (trial, individual, occasion)
  - Generates random variables form parametric continuous or discrete distributions (Normal, Uniform, Log-Normal, Binomial)
  - Accounts for correlation in random variables

Patient-Level vs Population-Level Simulations

Patient-Level simulations

- Each simulation replicate corresponds to a virtual patient
- Used to generate distributions of patient-level responses

Population-Level simulations

- Each simulation replicate corresponds to a virtual population (e.g. clinical trial, study arm, dose group, etc)
- Used to generate distributions of population-level responses (mean response, median survival, etc)
- Uncertainty must be incorporated to calculate prediction intervals of population-level summary statistics.

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Drug Property vs Clinical Trial Simulation

Drug Property Simulation

- Conducted to understand the properties of a drug
- “What is the probability of achieving Y response with X dosing regimen?”
- Independent of study design
- A large number of replicates are used to average out Monte Carlo noise

Clinical Trial Simulation

- Conducted to understand the performance of a potential trial
- “What is the probability of making the correct decision from this trial design?”
- Simulation design is dependent on a particular study design
- Number of replicates/patients may depend on study design

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When is Drug Property Simulation Necessary?

When the question to be answered is independent of trial design.

- What would the average steady-state concentration be for a 25 mg QD dose?
- What dose would be required to lower HbA1c by 1.4% in 80% of diabetic patients?
- What fraction of patients would meet efficacy criteria given the proposed dosing regimen?
- What is the probability that the adverse event rate would be below 30% in the proposed treatment population?

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When is Clinical Trial Simulation Necessary?

When the question to be answered concerns the trial design:

- Is the proposed PK sampling design sufficient for this trial?
- Which trial design is better for a proof of concept decision?
- What is the probability of accurately learning about the dose-response relationship, in a planned Phase 2b trial?
- What is the probability of being superior to our comparator if we change the inclusion criteria to baseline HbA1c >8.2%?

Parameter Uncertainty

Incorporated into a simulation to integrate over the uncertainty in model parameter values, when making probabilistic inferences.

- Provides transparent acknowledgment of the quality of data/information upon which the model was built.
- Provides a natural mechanism to assess sensitivity of conclusions to gaps in knowledge.

Sampled using Monte Carlo techniques to produce a set of population parameters (fixed & random effects) for each simulation replicate (population or trial).

Parameter Uncertainty

Important to preserve information on parameter correlations.

- NONMEM Covariance Matrix
  - Fixed effects sampled from multivariate normal distribution (e.g. MASS::mvrnorm)
  - OMEGAs sampled from inverse wishart distribution
- Bootstrap Analysis
  - Parameter sets sampled from bootstrap replicates
- Bayesian Posteriors
  - Parameter sets sampled from accumulation phase of Bayes estimation (NONMEM EXT file)

Precision and Model Parameterization

Parameter uncertainty (posterior) distribution assumptions should be consistent with plausible values for that parameter. For example:

```
CL = THETA(1)      V = THETA(2)
```

- Plausible values ARE NOT consistent with Multivariate Normal Distribution. CL and V must be positive.

```
CL = EXP(THETA(1))   V = EXP(THETA(2))
```

- Plausible values ARE consistent with Multivariate Normal Distribution. CL and V will always be positive.
- Variance terms can be similarly constrained, but gets messy.

Consider posteriors from MCMC Bayes or Non-Parametric Bootstrap for joint uncertainty distribution.

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Parameter Uncertainty Distributions (Bootstrap, Bayesian Posteriors)

simulation_examples.R × post ×

Filter

1 Full set of simulation parameters per row (1 row = 1 population)

	TVCL	TVVC	TVP1	TVP2	TVQ1	TVQ2	TVKA	TVVMAX	TVKM	TVFSC	TVKSYN	TVKDEG	TVIC50	OMEGA11	OMEGA21	OMEGA22	OMEGA31	OMEGA3
1	161.2	2806	608.8	224.9	15.430	3.030	0.01282	13380	6.913	0.0719	0.8992	0.01736	4.780	0.04322	0.002295	0.011480	0.002140	0.0(
2	166.5	2777	404.9	279.3	20										0158	0.010650	-0.001016	-0.0(
3	166.1	2734	445.5	268.5	15										1292	0.011340	-0.003702	-0.0(
4	164.7	2841	443.5	210.8	16.870	2.797	0.01306	16200	6.412	0.0719	0.8990	0.02042	5.392	0.04211	0.001097	0.011850	0.005942	-0.0(
5	164.4	2763	362.0	236.5	13.760	3.053	0.01299	11910	6.166	0.0719	0.8801	0.02057	4.719	0.03528	-0.002286	0.014440	0.001265	-0.0(
6	158.0	2774	492.8	269.7	18.710	3.243	0.01342	13330	7.231	0.0719	0.9111	0.01801	7.236	0.03875	0.000013	0.011000	-0.003638	0.0(
7	172.7	2762	393.0	162.3	17.030	3.469	0.01333	13880	7.603	0.0719	0.9166	0.02102	8.114	0.04001	0.005018	0.012030	-0.000242	0.0(
8	163.1	2798	428.5	275.7	22.890	3.516	0.01293	13330	5.620	0.0719	0.9045	0.02093	4.489	0.03880	-0.000460	0.010740	0.001528	-0.0(
9	163.6	2851	564.7	200.9	13.450	2.857	0.01274	11520	8.035	0.0719	1.0620	0.01962	4.970	0.03727	0.001250	0.007948	-0.001992	0.0(
10	170.4	2676	483.1	285.0	15.270	3.351	0.01252	11990	6.574	0.0719	0.8403	0.02221	3.825	0.03388	-0.002923	0.015150	0.001194	-0.0(
11	167.3	2694	563.7	220.8	11.160	3.220	0.01383	17220	6.553	0.0719	0.8845	0.02049	6.414	0.04906	0.003619	0.012220	-0.003930	0.0(
12	165.9	2811	449.0	337.0	16.110	2.221	0.01290	12030	6.649	0.0719	0.8536	0.02086	6.555	0.04665	-0.002264	0.014190	0.000123	0.0(
13	167.8	2815	489.9	277.3	13.320	3.298	0.01370	14530	5.624	0.0719	0.8843	0.01928	5.395	0.03927	-0.002070	0.011790	0.008396	0.0(
14	159.8	2867	407.7	272.7	16.290	3.410	0.01370	14880	7.152	0.0719	0.9224	0.02148	4.932	0.04118	0.001146	0.011190	-0.003192	-0.0(
15	161.4	2748	475.4	244.2	18.220	3.479	0.01380	13110	7.237	0.0719	0.8915	0.02027	6.843	0.04140	0.000122	0.009473	-0.000770	-0.0(
16	176.2	2792	584.3	285.5	17.410	3.833	0.01294	12590	6.490	0.0719	0.8110	0.02048	5.228	0.04308	-0.000648	0.009098	-0.001556	-0.0(
17	171.2	2891	489.7	304.9	17.980	2.845	0.01314	14530	5.326	0.0719	0.8663	0.02111	4.954	0.04570	-0.001761	0.011100	-0.000187	0.0(
18	166.5	2716	596.3	259.2	14.660	3.041	0.01241	13360	6.524	0.0719	0.8924	0.01938	5.047	0.03846	-0.002433	0.011500	0.003315	-0.0(
19	171.2	2831	592.0	308.7	20.390	2.762	0.01417	13200	6.610	0.0719	0.9432	0.02159	5.649	0.04906	-0.002047	0.010660	-0.000913	0.0(
20	173.5	2772	472.3	225.5	17.470	2.372	0.01307	14010	7.902	0.0719	0.8685	0.01933	6.172	0.04865	0.001380	0.013980	-0.001973	0.0(

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Covariates

Patient characteristics (intrinsic or extrinsic) that affect model parameter values or other aspects of the simulation (dosing amounts for mg/kg regimens).

- Can be assigned to specific values to explore the impact of covariate effects.
- Can be sampled using Monte Carlo techniques to produce distributions of responses representative of a particular population.

Important to capture correlations between covariates to generate realistic virtual patients.

- Can be sampled from empirical distributions (multivariate), based upon previously observed patient data.
- Can be sampled from patient databases of observed patient data.

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Variability

Inter-individual variability

- Random variation in model parameters between individuals (virtual or otherwise)
- Sampled from empirical distributions defined by statistical model, with variance of OMEGA
- One sample per virtual patient

Inter-occasion variability

- Random variation in model parameters between defined occasions
- Sampled from empirical distributions defined by statistical model, with variance of OMEGA
- One sample per occasion (dosing event, clinic visit, ...)

Residual Unexplained Variability

For the purposes of simulation, RUV is essentially **observation error**.

- Do not include RUV if you are interested in what is happening in the system (e.g. what a patient's blood concentration actually is at a particular time)
- Include RUV if you are interested in what would be **observed** about the system (e.g. what blood concentration would be measured at a particular time)

- Sampled from empirical distributions defined by statistical model, with variance of SIGMA
- One sample per observation
- For models with multiple endpoints (e.g. PK/PD), it may be important to capture correlation in residual variability (SIGMA BLOCK).

Most Common Types of Simulation

Type	Replicate	Uncertainty	IIV/IOV	RUV	Output	Usage
Deterministic	1 Patient	No	No	No	Typical response for a population or predicted response for specific individuals.	Used for illustration or to generate predictions for specific individuals.
Variability	1 Patient	No	Yes	Yes*	Distribution of likely patient-level responses, ignoring uncertainty.	Used for illustration and interpolation.
Uncertainty	1 Population	Yes	No	No	Distribution of probable typical responses, given uncertainty in parameter estimates.	Used for making probabilistic statements about typical response.
Probabilistic	1 Patient	Yes	Yes	Yes*	Distribution of probable patient responses, given uncertainty in parameter estimates.	Used for making probabilistic statements about patient-level responses.
Population	1 Population	Yes	Yes	Yes*	Distribution of probable summary statistics given uncertainty in parameter estimates.	Used for making probabilistic statements about population-level responses.

*Residual unexplained variability is included if desired simulation output is what would be **observed**.

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Outline

- Basic Simulation Concepts
- **Construct Simulation Map**
- Implement Simulation
- Sensitivity Analysis

Introducing the Simulation Map™

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)			
Population/Trial (p)			
Individual (i)			
Occasion (k)			
Observation (t)			

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Simulation Map for Simple PopPK Simulation

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)			
Population/Trial (p)	CL V Ω Σ NHANES	30 mg single-dose at 0, 0.5, 1, 2, 4, 8, 12, 16, 20, 24 hours	1
Individual (i)	η_{CLi} η_{Vi} Wt_i AGE_i CL_i V_i		1000
Occasion (k)			1
Observation (t)	$Conc_t$ ε_t		10

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Simulation Map for PopPK Simulation w/ IOV

	Model Parameters, Measurable & Uncontrollable Factors	Design	N
Uncertainty (u)			
Population/Trial (p)	CL V Ω Σ NHANES	30 mg multiple-dose at 0, 0.5, 1, 2, 4, 8, 12, 16, 20, 24 hours	1
Individual (i)	η_{CLi} η_{Vi} Wt_i AGE_i CL_i V_i		1000
Occasion (k)	CL_{ik} η_k	Week 1, 2, 4, 8	4
Observation (t)	$Conc_t$ ε_t		10

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*Residual unexplained variability is included if desired simulation output is what would be **observed**.

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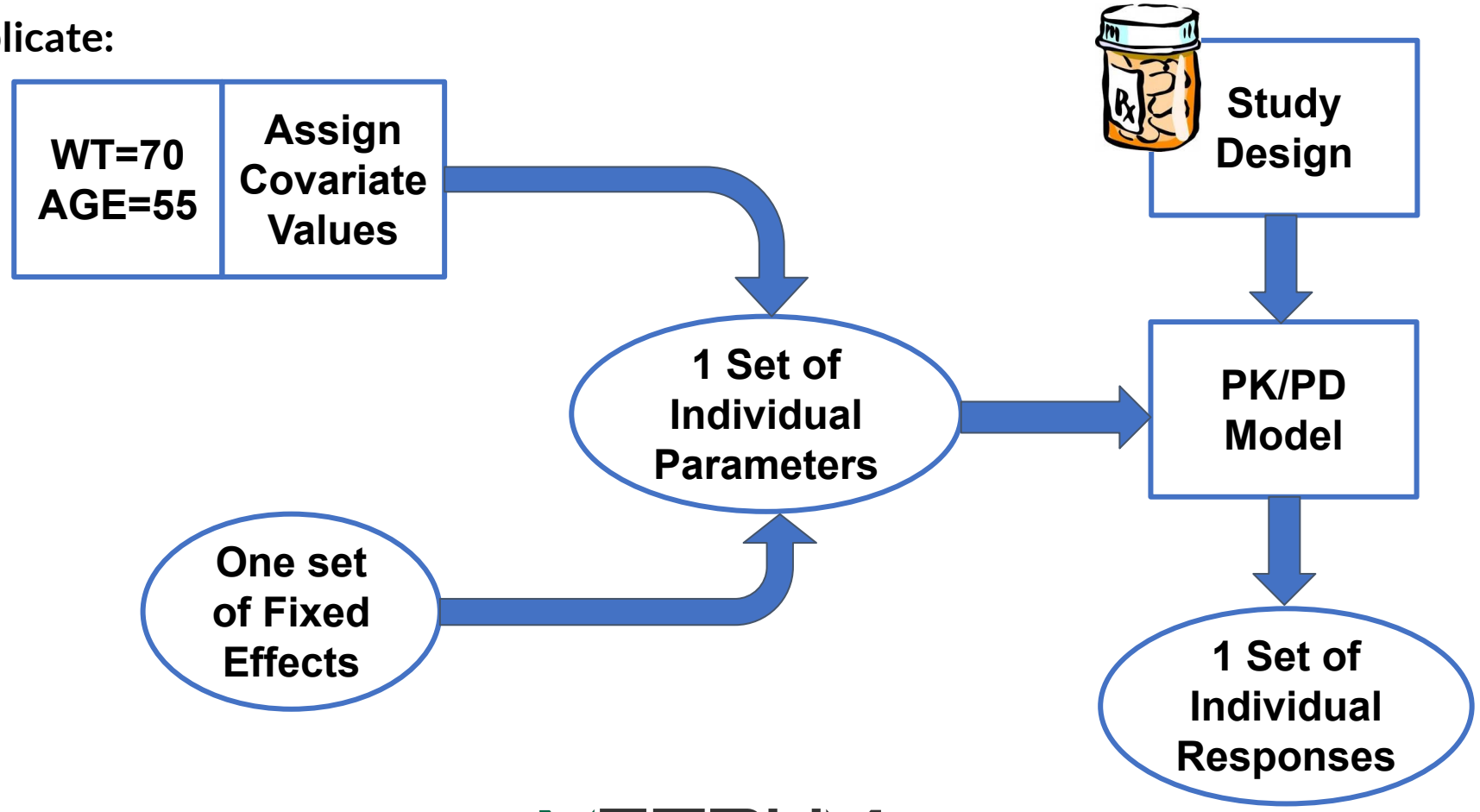
Deterministic Simulation

Simulate using only fixed effects for illustration or to generate predictions for specific individuals.

For each replicate:



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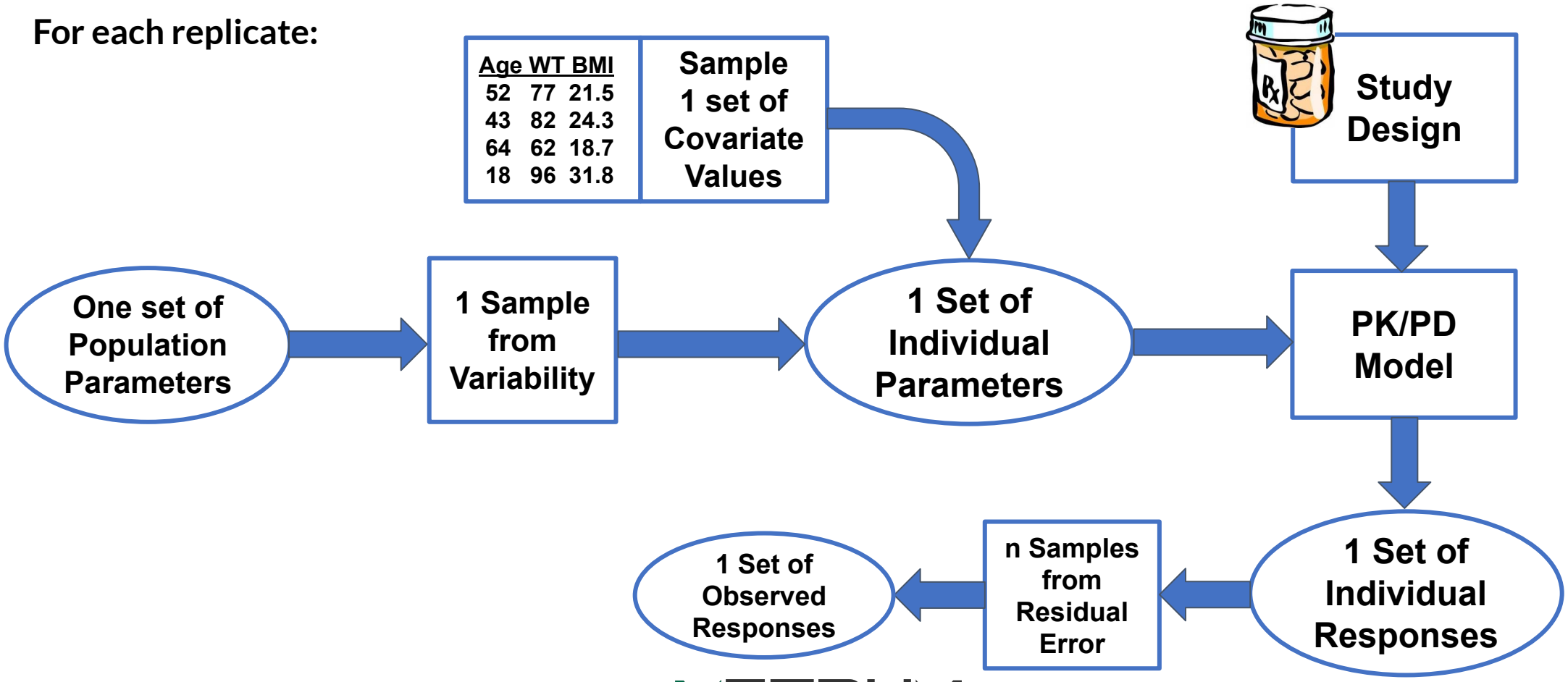
Simulation with Variability

Simulate with variability, to understand the distribution of predictions in a group of patients.

For each replicate:



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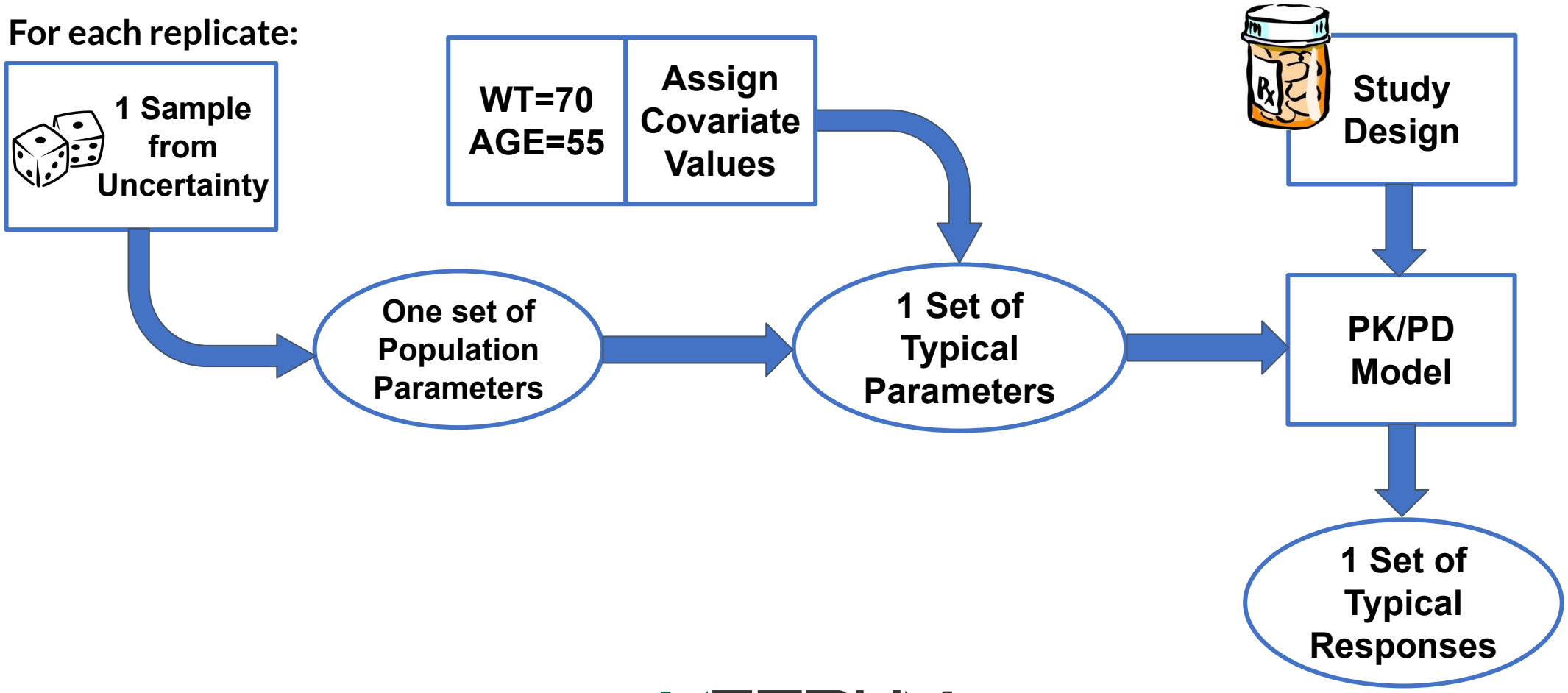
Simulation with Uncertainty

Simulate with uncertainty, to understand the probable distribution of typical responses.



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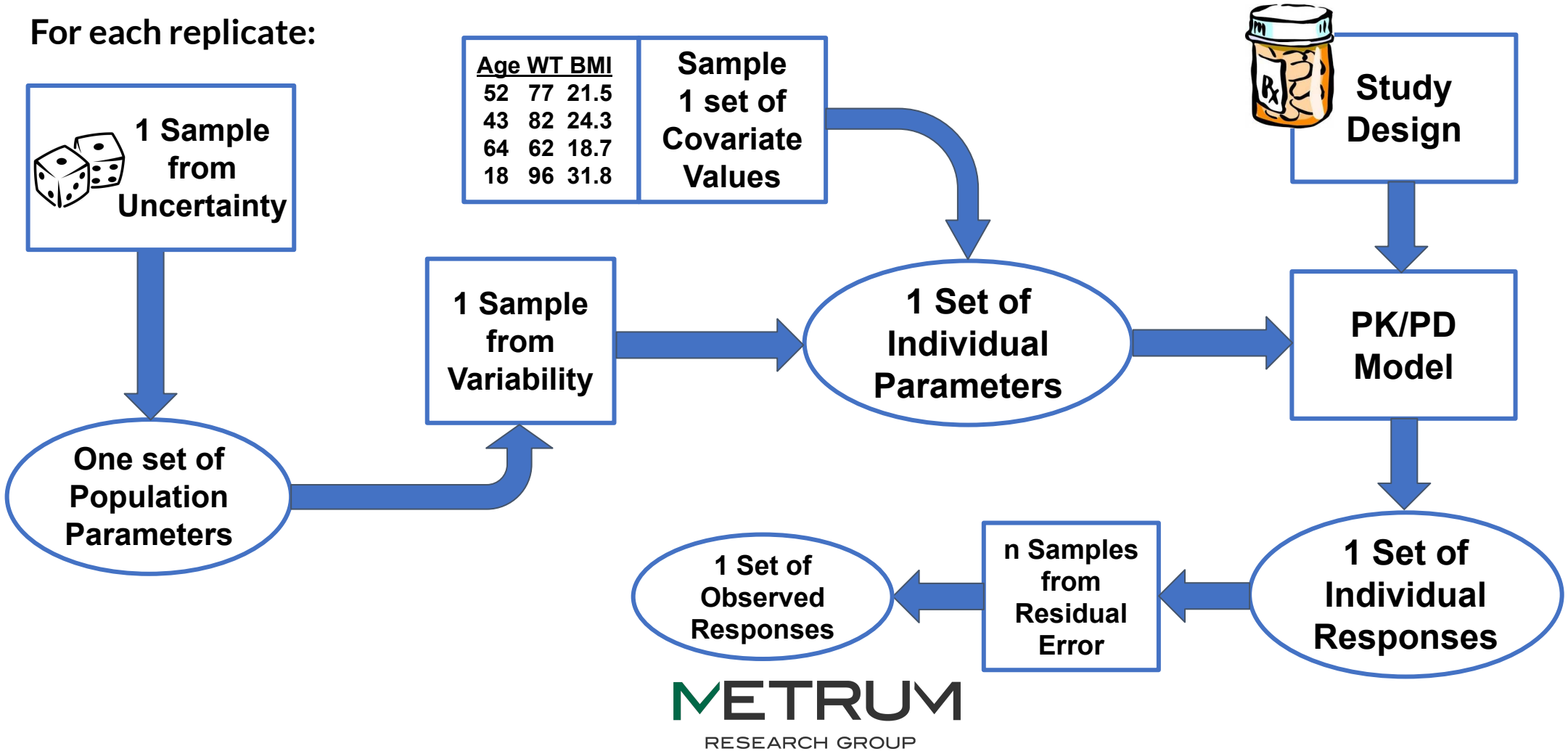
Probabilistic Simulation

Simulation with uncertainty and variability, to understand the probable distribution of patient responses.

For each replicate:



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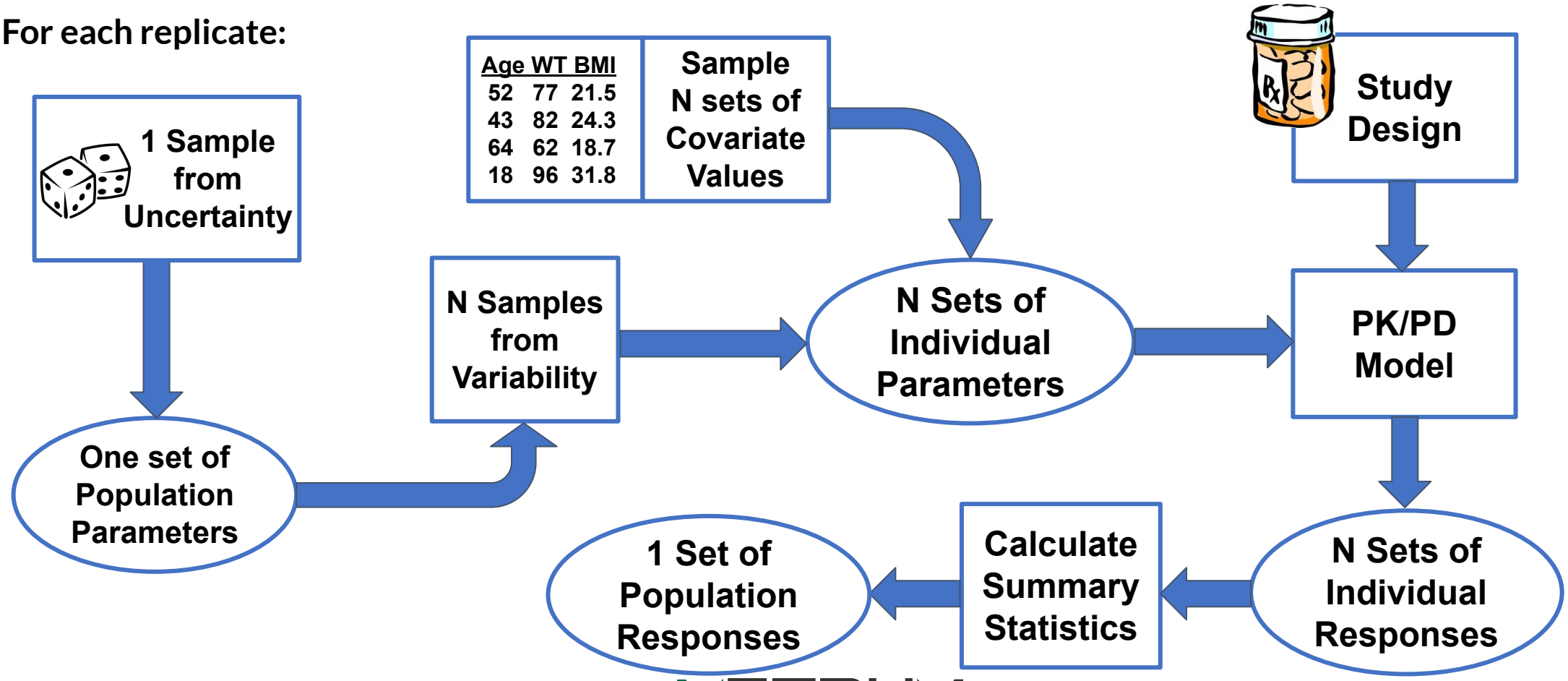
Population Simulation

Simulation with uncertainty and variability, to understand the probable distribution of population responses.

For each replicate:



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Outline

- Basic Simulation Concepts
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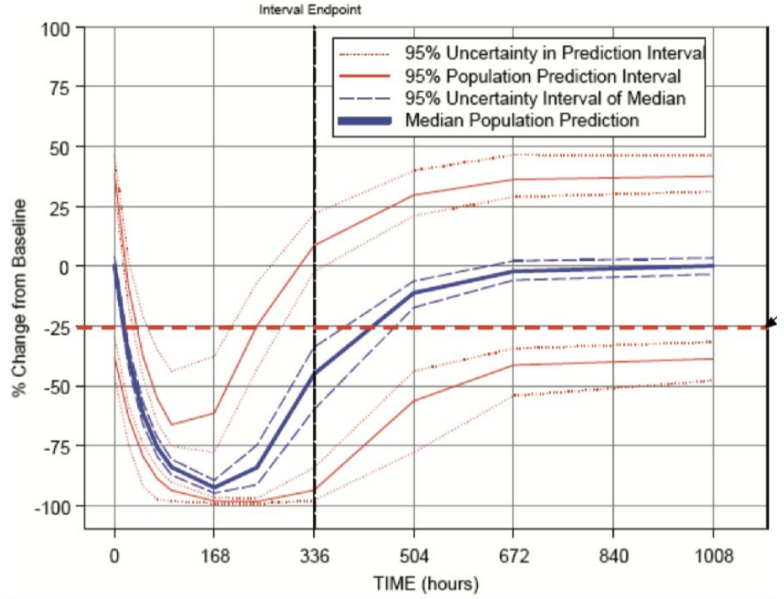
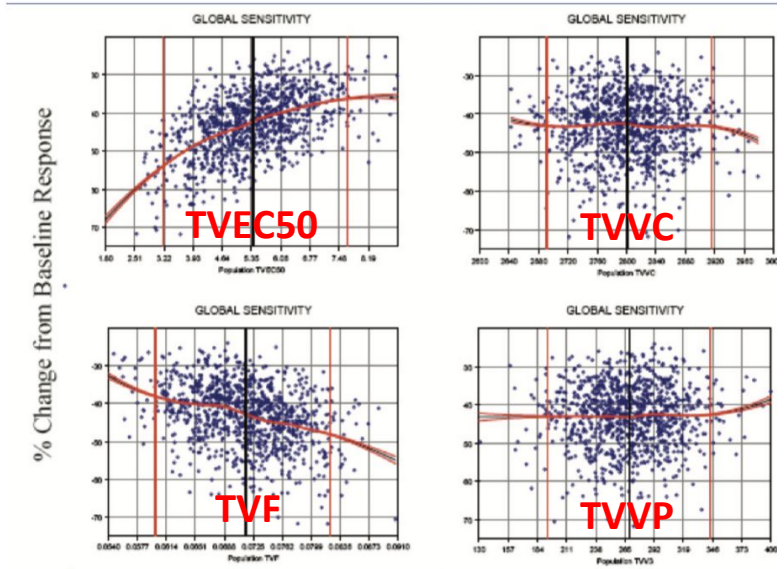
- **Sensitivity Analysis**

Parameter Uncertainty and Global Sensitivity Analysis

- Start with simulations including parameter uncertainty
- Explore sensitivity of simulation outcomes (conclusions) to range of parameter uncertainty
- Are conclusions robust to lack of knowledge?





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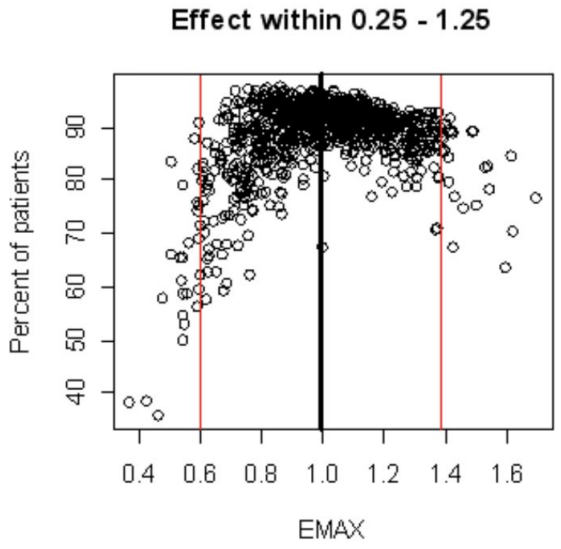
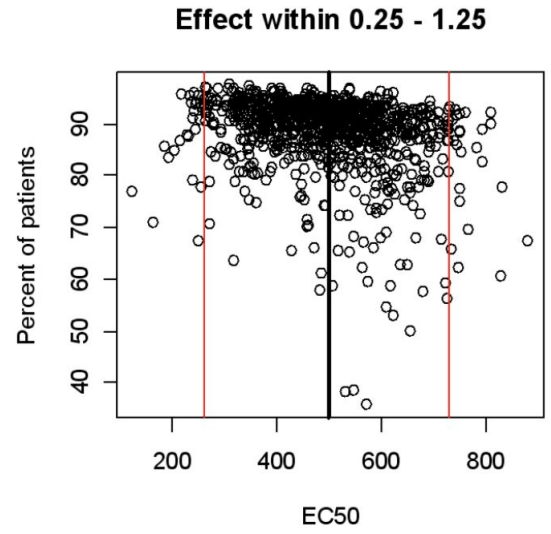
Uncertainty in PD Parameters & Sensitivity Analysis





Question: Can we get 80% of patients within target trough effect range at this dose?

- Conclusions depend on the value of EMAX.
- Precise knowledge of EMAX is very important to answer this question.
- Uncertainty in EC50 is less important than uncertainty in EMAX

Black: median Red: 95% CI

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the end

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