# Clinical Trial Simulations With Uncertainty

## Application using `simpar`

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# Parameter uncertainty is defined as “how well the population parameters (THETA, OMEGA and SIGMA) are known or estimated”

- **Quality of data:**
  If clearance (CL) estimation has high uncertainty, this could mean: - Limited data in certain patient populations - Sparse sampling in elimination phase

- **Critical for making probabilistic statements**
  For a proposed dosing regimen: Without uncertainty: "Predicted Cmax is 500 ng/mL"
  With uncertainty: “Predicted typical value 500 ng/mL (400 - 600 ng/mL) mean [95%CI]

- **Identify knowledge gap**
  If uncertainty in EC50 greatly affects efficacy predictions: May need additional dose-ranging studies and could influence go/no-go decisions.

**Table 2.** Phosphoramide Mustard Population Pharmacokinetic Final Parameter Estimates With SIR Results

| Parameter | Estimate (RSE%) | BSV% (RES%)[shrinkage%] | SIR Median (95%CI) | BSV SIR% (95%CI) |
|---|---|---|---|---|
| $Cl_R$ (L/h)[a] | 14.9 (9.3) | 39.8 (10.5)[6.8] | 14.8 (11.8-17.7) | 40.3 (31.6-48.6) |
| $Cl_R \sim$ W power[b] | 0.75 | … | … | … |
| $Cl_R \sim$ CrCL power[b] | 1 | … | … | … |
| $V_c$ (L)[c] | 525 (3.8) | 32.9 (8.4)[1.7] | 525 (489–564) | 33.2 (28.3–38.2) |
| Vc ~ W power[b] | 1 | | | |
| $K_{TR}$ ($h^{-1}$)[c] | 1.3 (6.7) | 27.3 (19.0)[32.0] | 1.3 (1.2–1.5) | 27.5 (20.2–33.8) |
| $K_{TR} \sim$ W power[b] | 0.25 | … | … | … |
| $V_{Max}$ (mg/h)[c] | 81.2 (6.3) | … | 81.6 (68.4–95.7) | … |
| $V_{Max} \sim$ W power[b] | 0.75 | … | … | … |
| $K_M$ (mg/L) | 0.51 (15.4) | 29.0 (27.8)[58.2] | 0.52 (0.33–0.75) | 29.0 (16.2–38.8) |
| $RUV_{Prop}$ (%) | 9.7 (11.5) | … | 9.8 (8.3–11.6) | … |
| $RUV_{Add}$ (ng/mL) | 54.9 (10.9) | … | 54.9 (42.2–67.8) | … |

BSV, between-subject variability; $Cl_R$, renal clearance; KM, concentration at half of $V_{max}$; KTR, formation rate constant; RSE, relative standard error; RUV, residual unexplained variability for proportional (prop) and additive (add) error models; Vc, volume of distribution; VMax, maximum velocity.
[a] For 70 kg person with CrCL of 85 L/min.
[b] Fixed values.
[c] For 70-kg person.

https://accp1.onlinelibrary.wiley.com/doi/epdf/10.1002/jcph.2144

# How can we assess parameter uncertainty?

Different methods exists:

1. NONMEM Asymptotic covariance matrix (`$COVARIANCE`)
2. Non-parameteric bootstrap: resample your data with replacement: `PsN, R, NONMEM`
3. Sampling from Bayesian posterior: `METH=BAYES` or `MCMC`
4. Others?

# Sampling distributions

- **Multivariate normal distribution**
  - Suitable for fixed-effect parameters: THETA
  - Preserve correlation structure
  - Symmetrical around the mean.
  - Without modeled correlation a full covariance matrix cannot be simulated
- **Inverse Wiahart distribution**
  - Suitable for variance parameters: OMEGA, SIGMA
  - Jointly sample variance and correlations
  - Always produce positive-definite matrices
  - Conjugate-prior to multivariate distribution
  - High degrees of freedom will result in less uncertainty. What that tells in for small sample size?

Ånother method is known as **LKJ** which deals with variances and correlation separately

```
library(MASS)
nsim <- 1000
theta_est <- c(1.5, 0.8)  # parameter estimates
cov_mat <- matrix(c(0.04, 0.01, 0.01, 0.02), 2, 2)
samples <- mvrnorm(nsim, theta_est, cov_mat)
```

```
library(MCMCpack)
nsim <- 1000
df <- 100 # number of subjects
omega_est <- matrix(c(0.2, 0.05, 0.05, 0.15), 2, 2)
omega_samples <- replicate(nsim, riwish(df, omega_est),
                           simplify = FALSE)
```

# Live demonstration: `simulation-1.R`

# simpar

Main function in the package is **simpar**!!

```
simpar(
  nsim,
  theta,
  covar,
  omega,
  sigma,
  odf = NULL,
  sdf = NULL,
  digits = 4,
  min = -Inf,
  max = Inf
)
```

```
#>      TH.1  TH.2   TH.3   OM1.1   OM2.2     OM3.2   OM3.3   SG1.1  SG2.2
#> 1   14.13 77.63 1.0640 0.10390 0.04442  0.007829 0.03910 0.03569 1.0690
#> 2   12.98 74.21 1.2430 0.09322 0.05781  0.048300 0.07054 0.04070 1.0910
#> 3   12.59 75.60 0.9816 0.11000 0.06001  0.009597 0.03225 0.04675 1.0330
#> 4   13.38 69.56 1.4090 0.11790 0.10790  0.061510 0.06000 0.03660 0.9531
#> 5   13.18 74.26 0.8007 0.11190 0.08363  0.046380 0.07052 0.04134 1.2040
#> 6   12.40 73.30 0.7659 0.09395 0.03944  0.017340 0.07900 0.03551 0.9038
#> 7   13.02 78.48 0.7257 0.08317 0.05386  0.027630 0.04757 0.04314 0.8023
#> 8   13.11 70.69 1.1650 0.08464 0.04884  0.041840 0.08535 0.04101 0.8885
#> 9   12.07 80.26 0.3608 0.10420 0.03331 -0.006786 0.06227 0.03728 0.8611
#> 10 19.73 74.93 2.5130 0.06927 0.06935  0.050570 0.05766 0.03791 0.9706
```

# Implementation in simpar: `ex-1.R`

Drug X is a novel small molecule being developed for Disease Y. Phase 1a/1b studies have been completed with single doses of 100, 150, and 250 mg in healthy volunteers and a small cohort of patients (Phase 1b). The drug showed a promising safety profile and preliminary efficacy signals. The target concentration for efficacy has been established as 500 mg/L based on preclinical studies.

The development team needs to select an optimal dose for Phase 2 studies. You have been provided with a population PK model (`106.mod, 106.cpp`) developed from Phase 1 data, including parameter estimates and their uncertainty.

1. Given the uncertainty in model parameters, characterize the typical concentration-time profiles for each dose level (100, 150, 250 mg). What is the 90% confidence interval around these profiles. Calculate typical AUC0-24 and Cmax with 5th and 95th around the typical value.

2. What is the probability that individual patients will maintain concentrations above the target threshold of 500 mg/L at 12 hours post-dose for each dose level? Consider both parameter uncertainty and between-subject variability in your analysis. How does this impact dose selection?

3. What is the probability that patients will have an **observed** concentrations above the target threshold of 500 mg/L at 24 hours post-dose for each dose level? Consider both parameter uncertainty, between-subject variability and residual unexplained variability in your analysis. How does this impact dose selection?