Acknowledging and Incorporating Uncertainty in Model-Based Inferences

ECPAG

July 24 & 25, 2006

Rockville, MD

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Overview

Acknowledging uncertainty in simulation parameters/models:

- Why?
  - Value of the approach
  - Some examples
- How?
  - Methods / Considerations
  - Useful features of simulation tool
  - Some available tools
- NMSUDs: new tool integrating R and NONMEM®

Uncertainty in Models & Parameters

- CTS employ models and parameter values based on a variety of prior information sources and assumptions
- CTS often involve extrapolations to unobserved conditions

Problem: Substantial uncertainty can exist in the models and parameters used for CTS.

A Solution: Acknowledge the uncertainty by formal incorporation in the simulation process.

Why Include Uncertainty in M&S?

- When uncertainty is not included, simulation results are only valid if the model and parameters are truth.
- Including uncertainty allows for a quantitative evaluation of the current state of knowledge

  e.g. How confident are you in the simulation results?
- View simulation outcomes as a probability distribution; conditioned on current knowledge
- Results in Global Sensitivity Analysis of simulation outcome dependence on parameter (model) assumptions

  e.g. What's the impact of model deficiencies?

Example 1: Optimal Design of a Pediatric Trial Using Simulations with Uncertainty

In collaboration with John Mondick, Jeff Barrett

The Children's Hospital of Philadelphia

Objectives of the Simulation Study

- To design a pediatric trial given the practical limitations
  - Sparse sampling
  - Time windows that patients are available for sampling

- To power the study to be able to estimate clearance for children < 1 year with sufficient precision and accuracy

Range of Practical Limitations for Trial Design

- 100-200 patients
- Age: 0-18 years
- Dosing: combination of Drug 1 and Drug 2
- Sparse sampling: three samples no later than 6 hours post-dose; one sample at 24-30 or 48-96 hours post-dose.

Specific Aims

- Select sampling times to characterize the population PK model
- Select number of patients sufficient to estimate the parameters with the desired precision
- Select proportion of patients with AGE < 1 year to sufficiently estimate age effect with the desired precision and accuracy

Models

- Drug 1: Three-compartment model parameterized in terms of CL, Q1, Q2, V1, V2 and V3. Characteristic half-lives: 10 minutes, 2 hours, 2 days

- Drug 2: Two-compartment model parameterized in terms of CL, Q, V1, and V2. Characteristic half-lives: 10 minutes, 2 hours

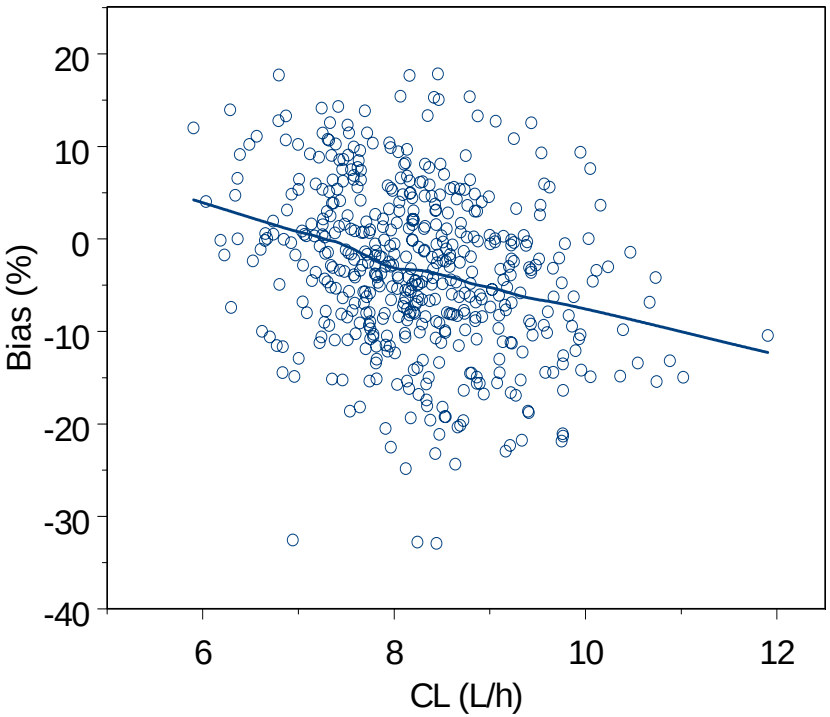
Initial Study Design

- n=200
- Group 1: 4 samples at
  - 5 to 15 minutes
  - 0.75 to 1.5 hours
  - 3.5 to 4.5 hours
  - 48 - 96 hours (25% of patients)
- Group 2: 4 samples at
  - 15 to 30 minutes
  - 2 to 3 hours
  - 5 to 6 hours
  - 48 - 96 hours (25% of patients)

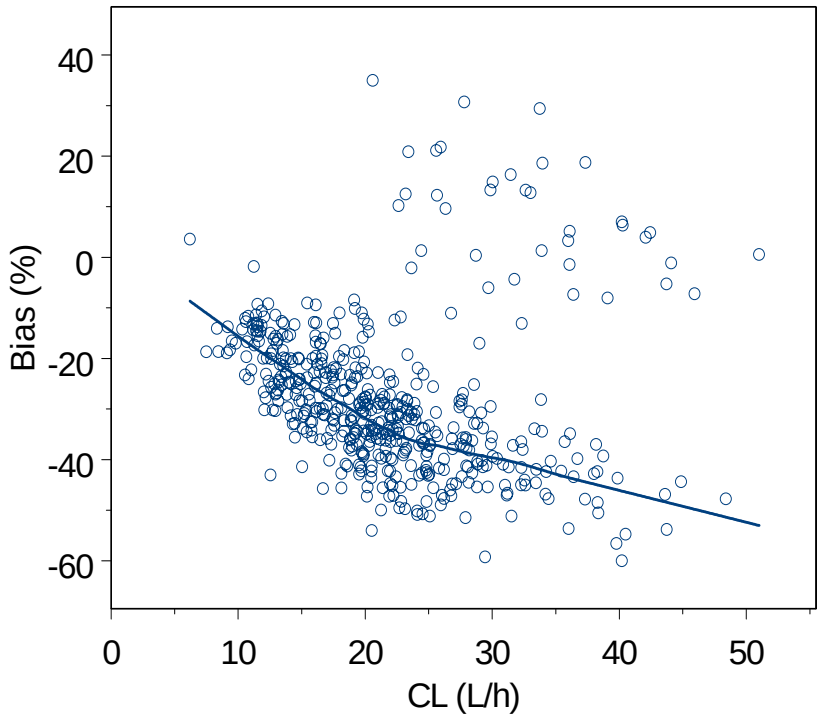
Initial design guided by D-optimality based on typical individual

Initial Design Results: CL

Drug 1

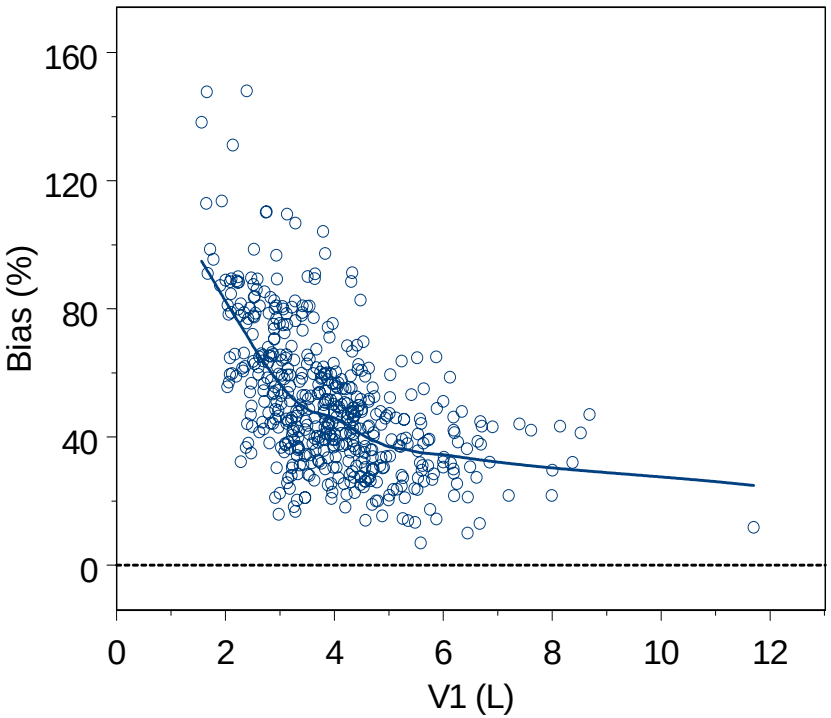


Drug 2

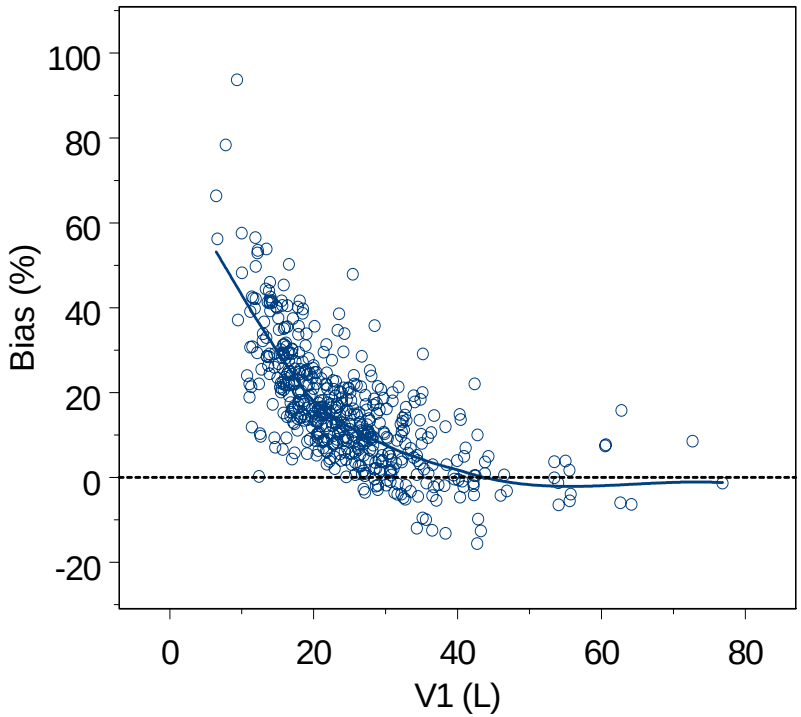


Initial Design Results: V

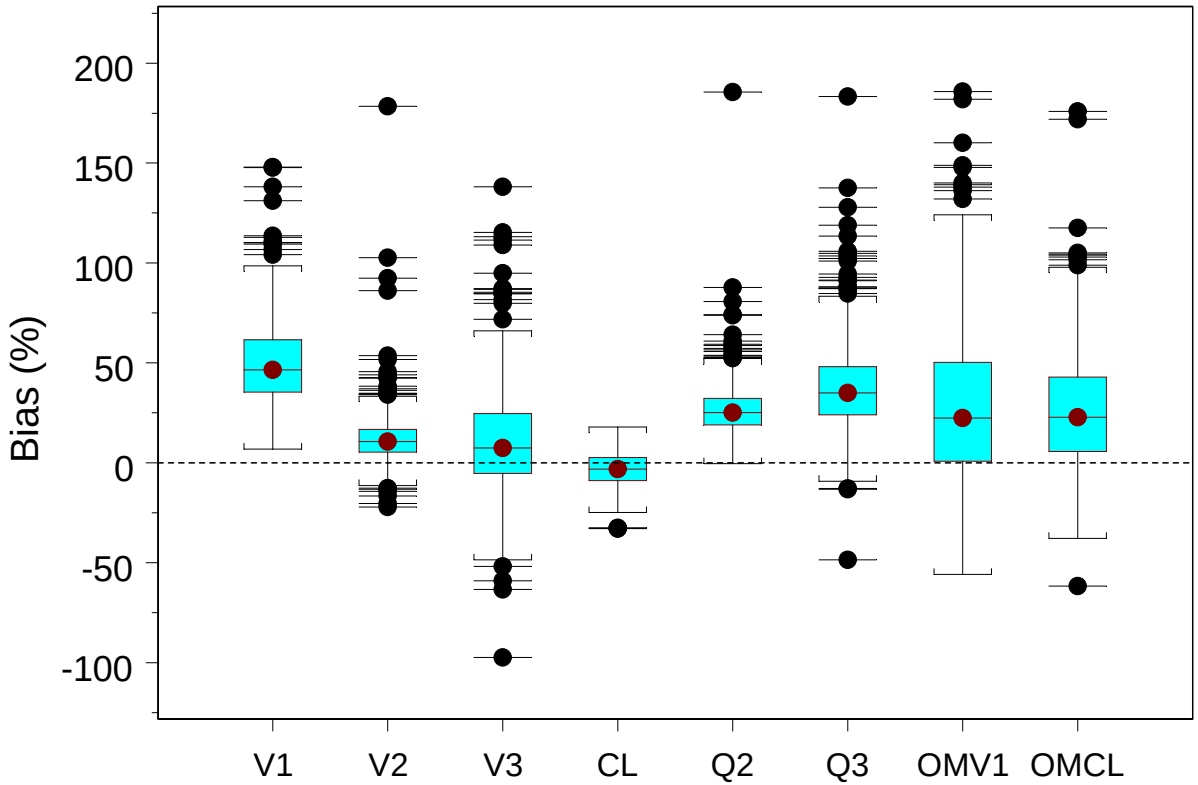
Drug 1



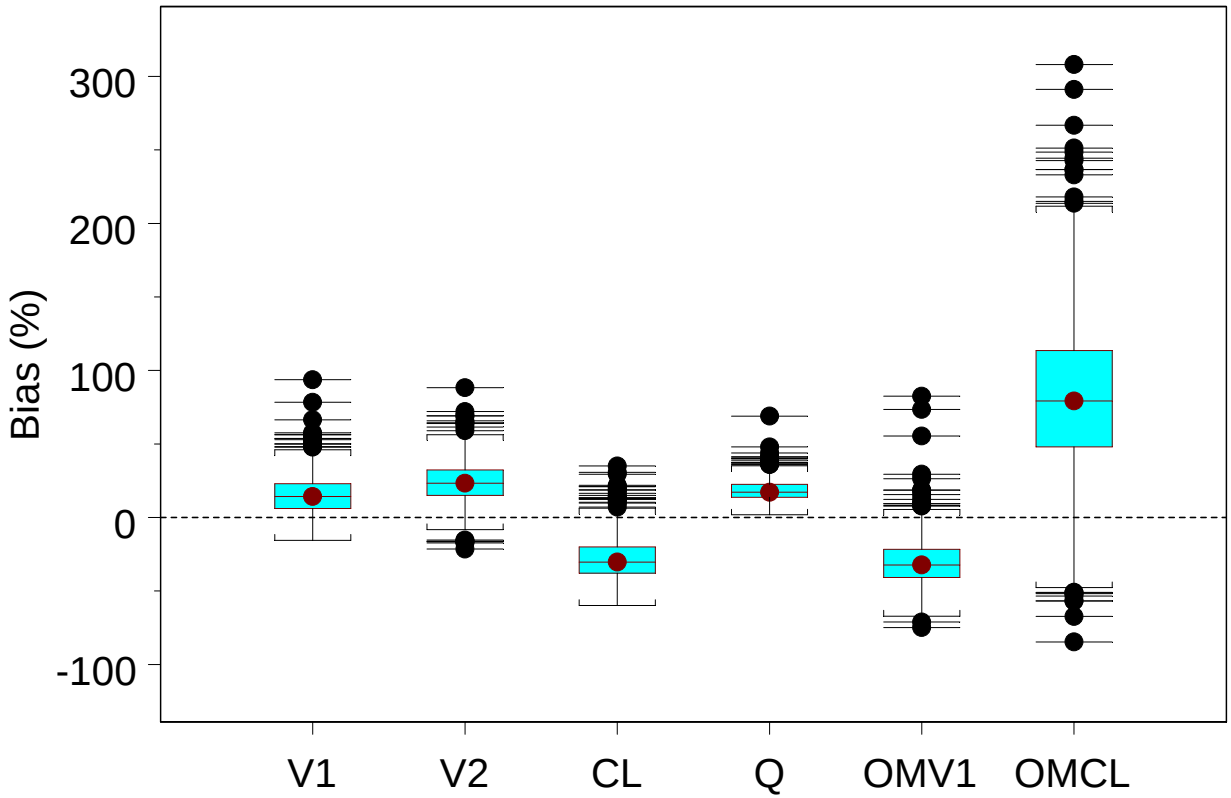
Drug 2



Initial Design Results: Drug 1 Bias



Initial Design Results: Drug 2 Bias



What to do?

- Improve our knowledge about population parameters (reduce uncertainty)

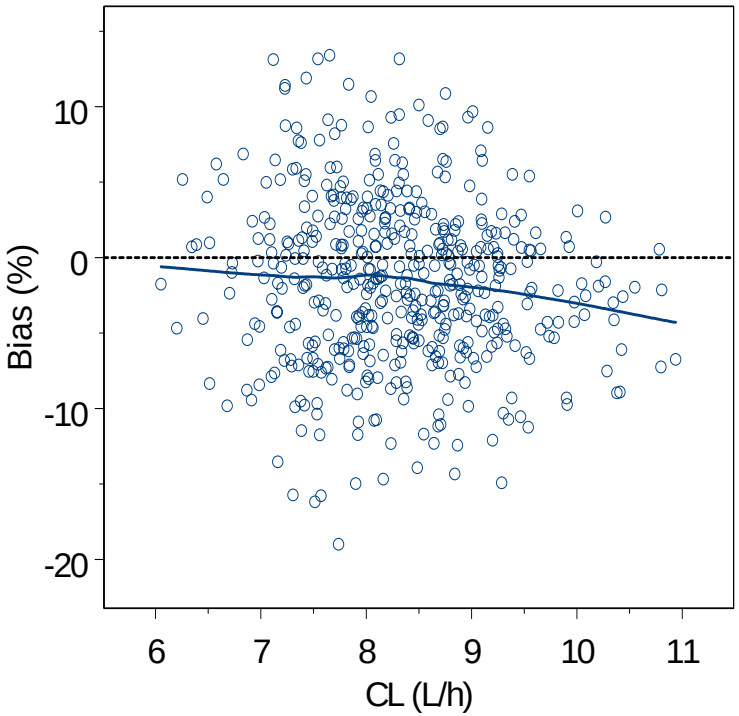
- Improve design to make it robust to the assumptions about the model parameters

Final Study Design

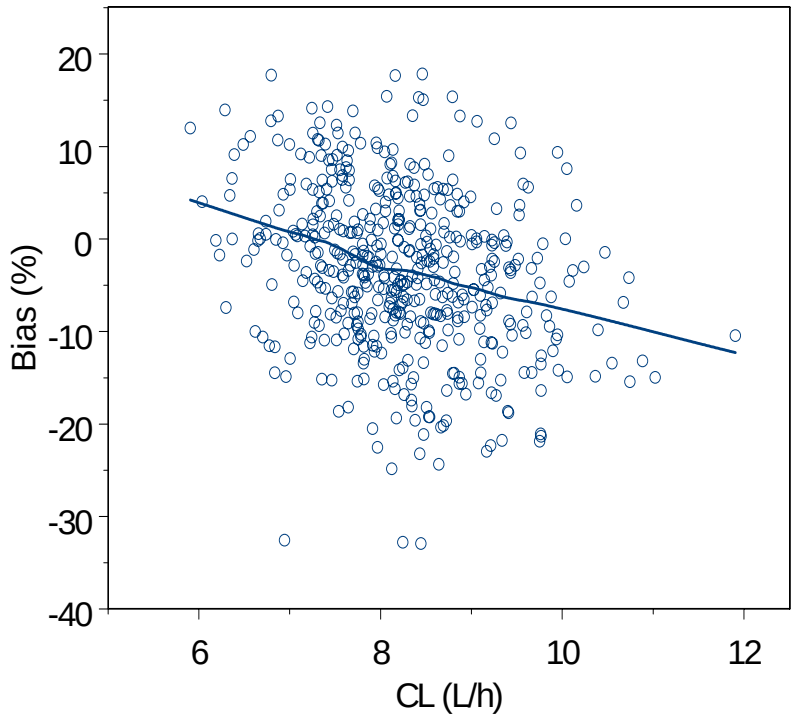
- 24 hour sample added in 50% of patients
- Patients with a sample collected 48 – 96 hours increased to 50%
- Sample fixed at 5 minutes included for both schedules
- Sampling windows adjusted for remaining times

Final Design Results: CL

Drug 1

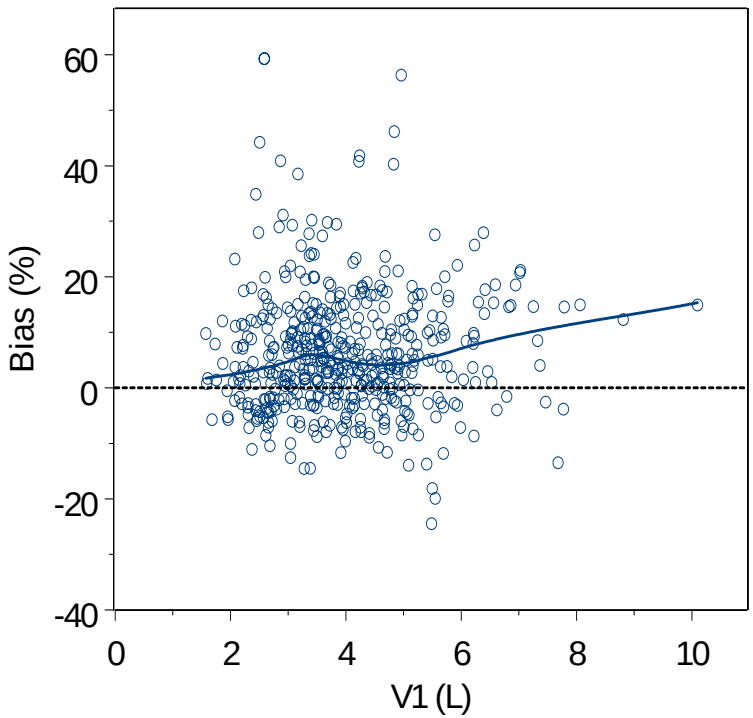


Drug 2

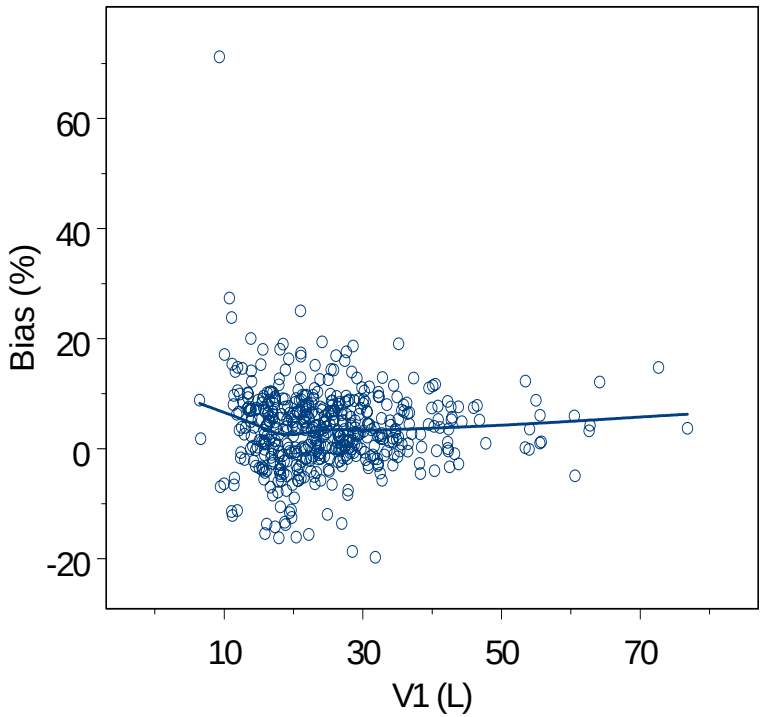


Final Design Results: V

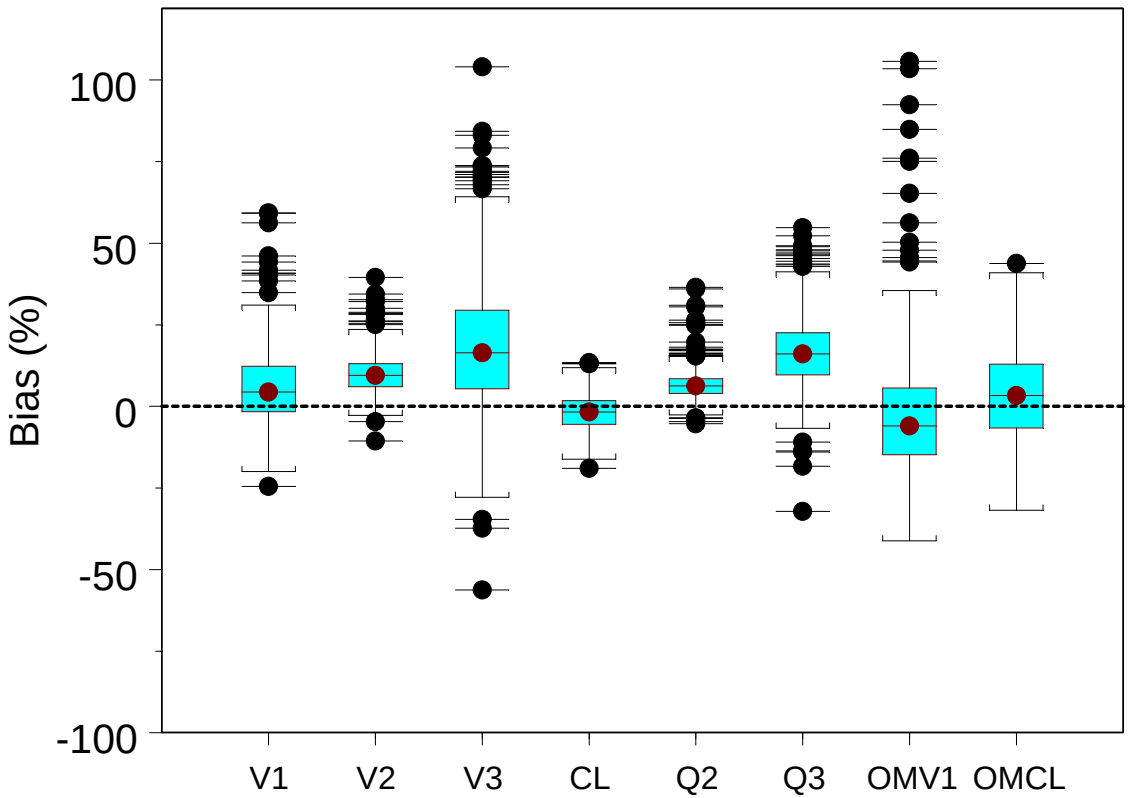
Drug 1



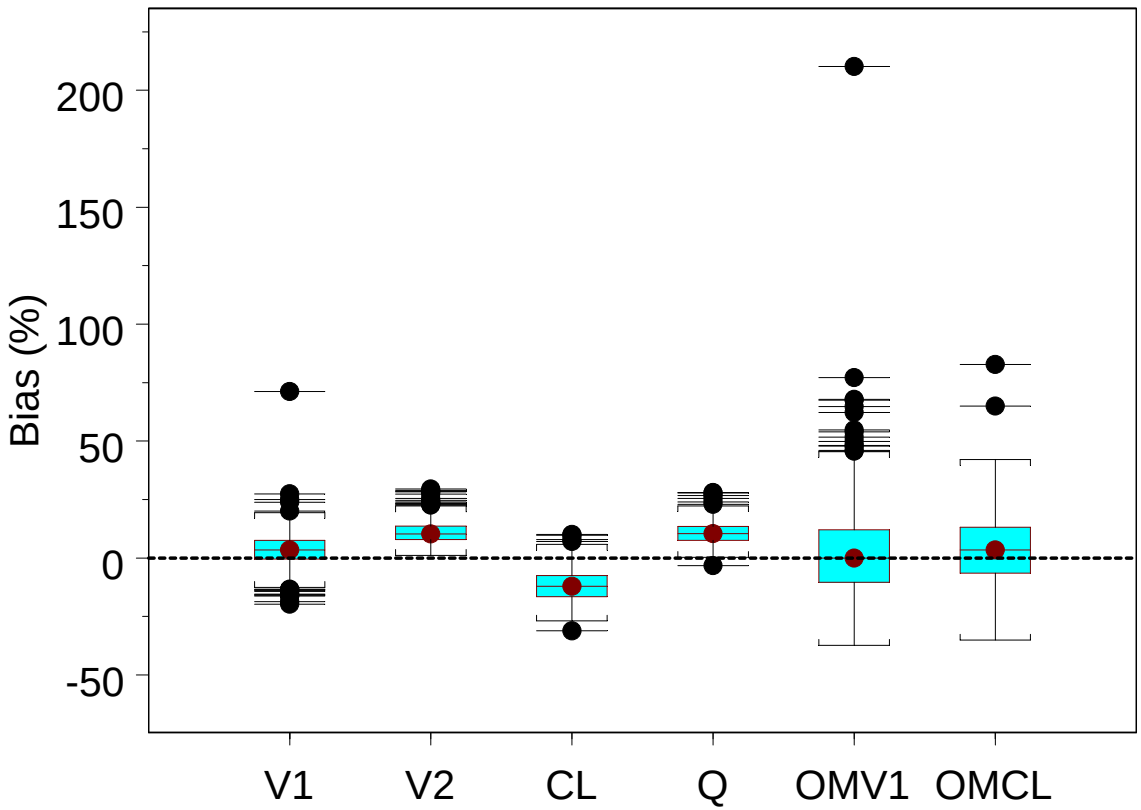
Drug 2



Final Design Results: Drug 1 Bias



Final Design Results: Drug 2 Bias



Conclusions

- Design was modified to make it robust to uncertainty across parameters
- Given the PK sample timing limitations, PK for both drugs could be accurately assessed
- 200 patients sufficient to characterize PK of both drugs
- 50 patients needed < 1 year old to characterize the suspected age effect on clearance

Example 2: Evaluation of Trial Design and Dose/Regimen Selection

Hypothetical Example

Specific Aims

Select dose

- To maximize % of patients with PD response at trough within a specific interval

Estimate (for a given design/dosing rule)

- % of patients with PD response at trough above and below the specified interval (goal = 90% of patients in target range)

Simulation Model

Study design:

- Oral administration
- Steady-state BID dosing
- 1000 patients

PK model:

- 3-compartment model;
- Terminal half-life ~ 30 hours

PK/PD model:

- direct Emax model

Simulations: Dose Selection Step

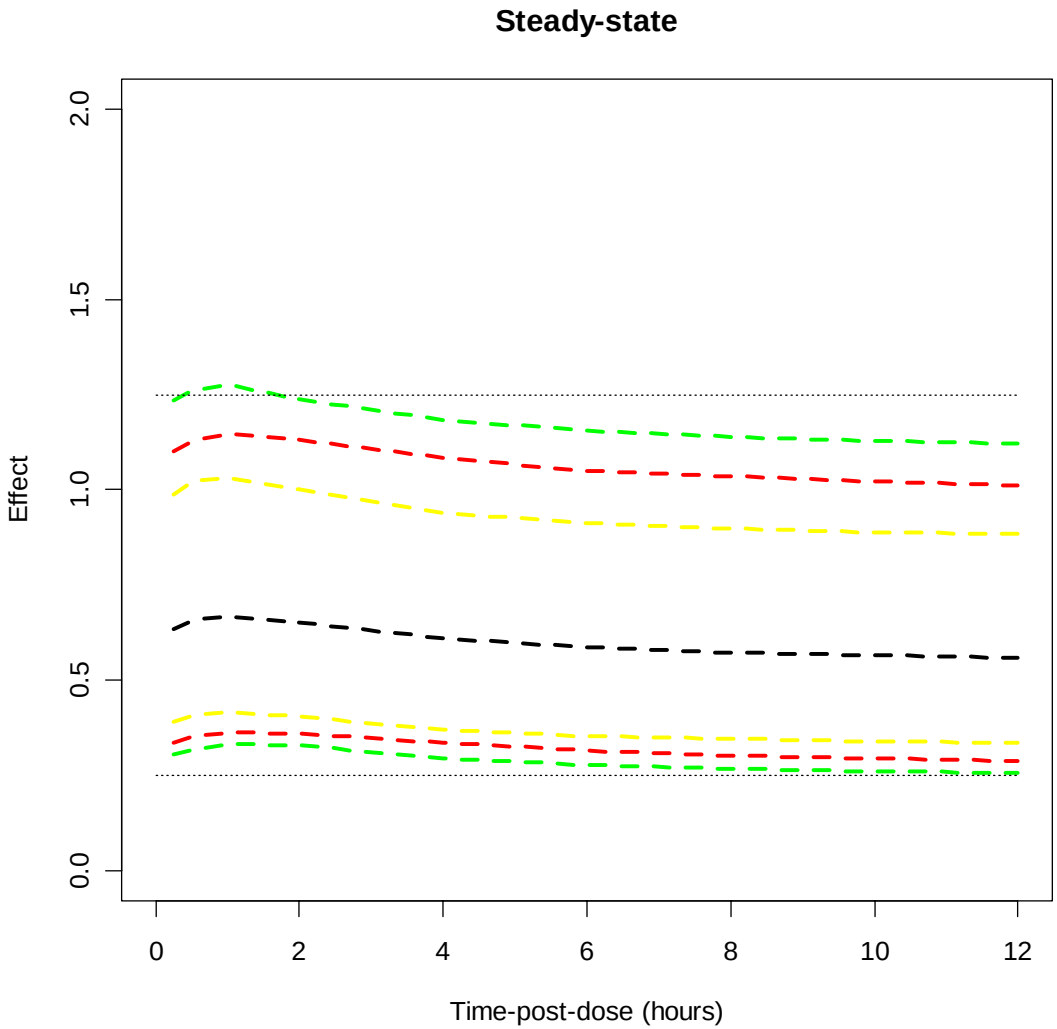
- Assuming perfect knowledge of population parameters, simulate study and compute expected endpoint values

- Assuming dose linearity, select the best dose that maximizes % of patients in the desired exposure range

Simulations: Sensitivity Analysis

- Conduct simulations with uncertainty to estimate range of possible outcomes
- Identify the most influential parameters
- Evaluate the effect of extra knowledge (decreased uncertainty)

No Uncertainty in Model Parameters

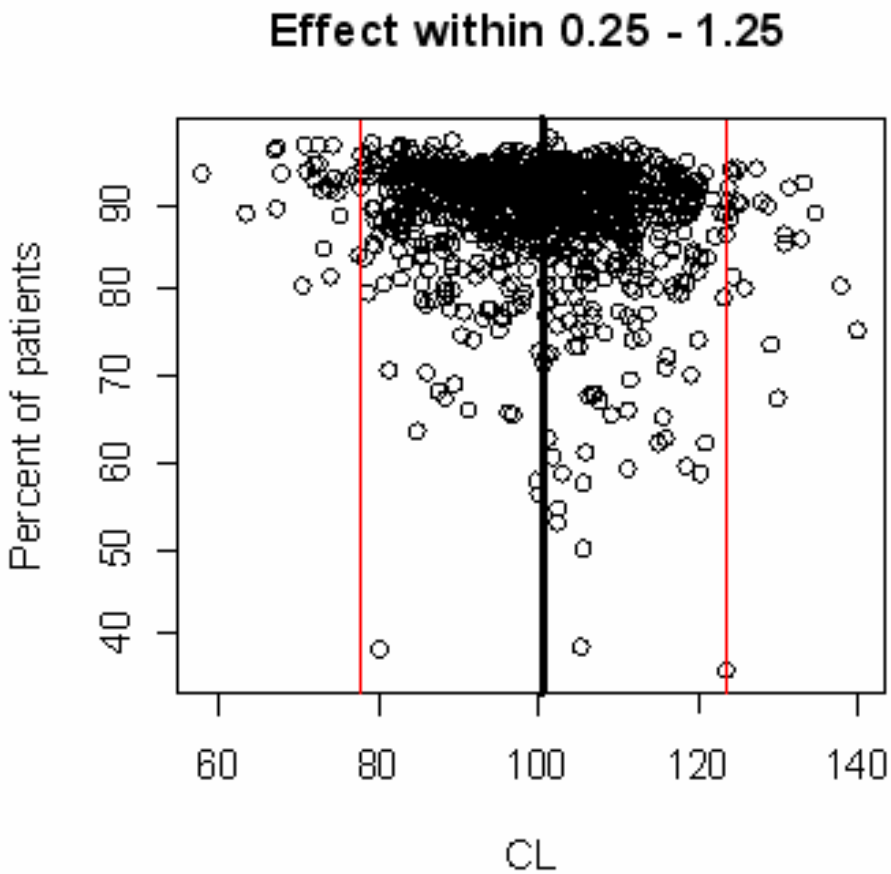


Effect-time course:

Black: median
Yellow: 80% CI
Red: 90% CI
Green: 95% CI

Dashed: desired range of trough effect (97% of patients were inside of this range)

Uncertainty in PK Parameters

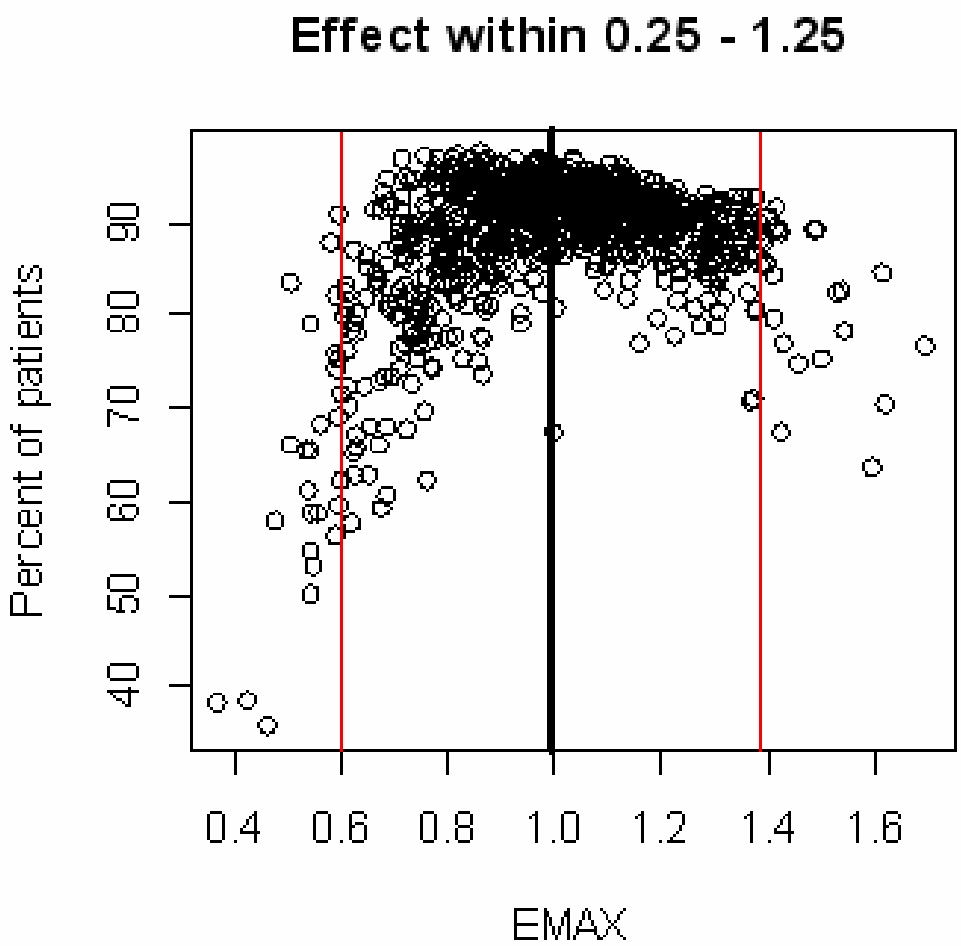


Effect of uncertainty in CL: % of patients with trough effect within the desired range

Simulated CL:
Black: median
Red: 95% CI

Conclusion: Uncertainty in CL is less important than uncertainty in PK/PD model parameters

Uncertainty in PD Parameters

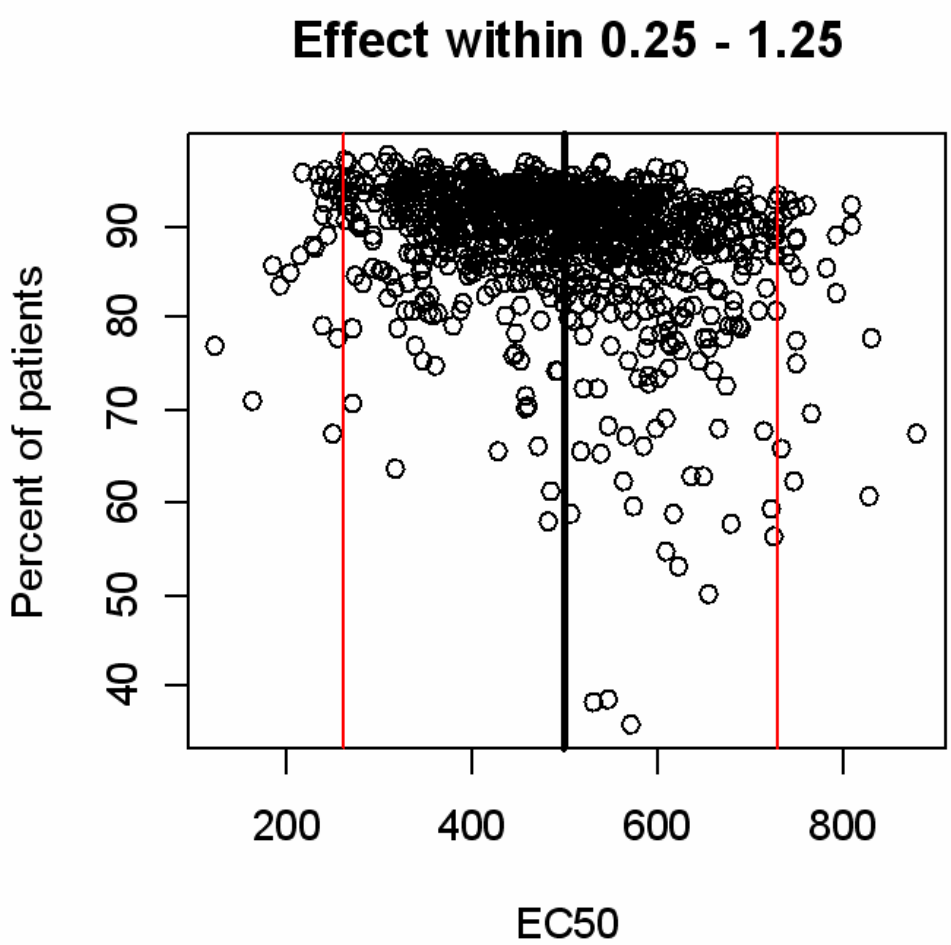


Effect of uncertainty in EMAX: % of patients with trough effect within the desired range

Simulated EMAX:
Black: median
Red: 95% CI

Conclusion: Precise knowledge of EMAX is very important

Uncertainty in PD Parameters



Effect of uncertainty in EC50: % of patients with trough effect within the desired range

Simulated EC50:
Black: median
Red: 95% CI

Conclusion: Uncertainty in EC50 is less important than uncertainty in EMAX

Conclusions for Example 2

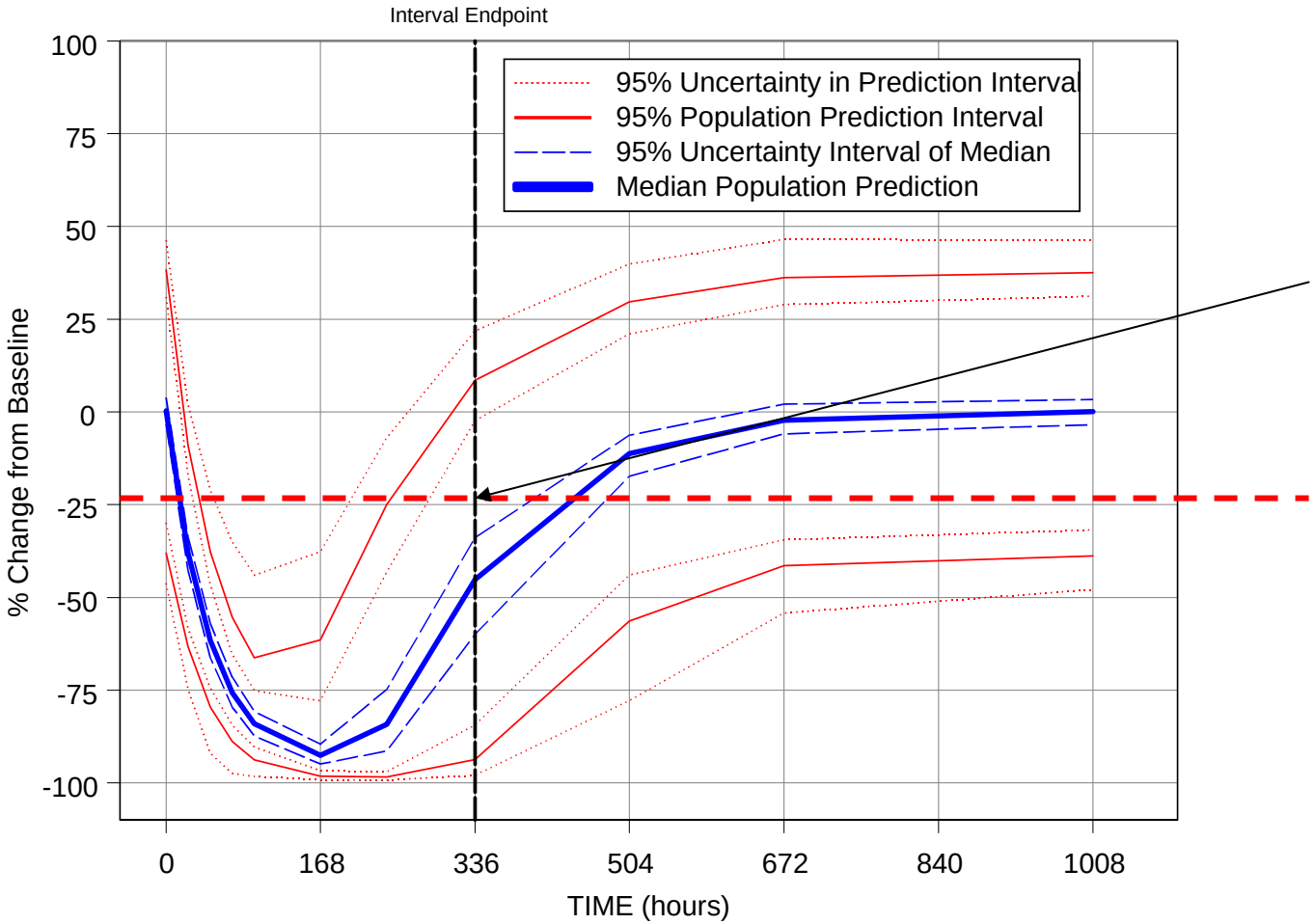
- When conditioned on current level of knowledge, this design results in:

  P(>90% of patients in target range) = 0.67

- Doses planned for the study are high enough so that exposure or EC50 are not as important as EMAX

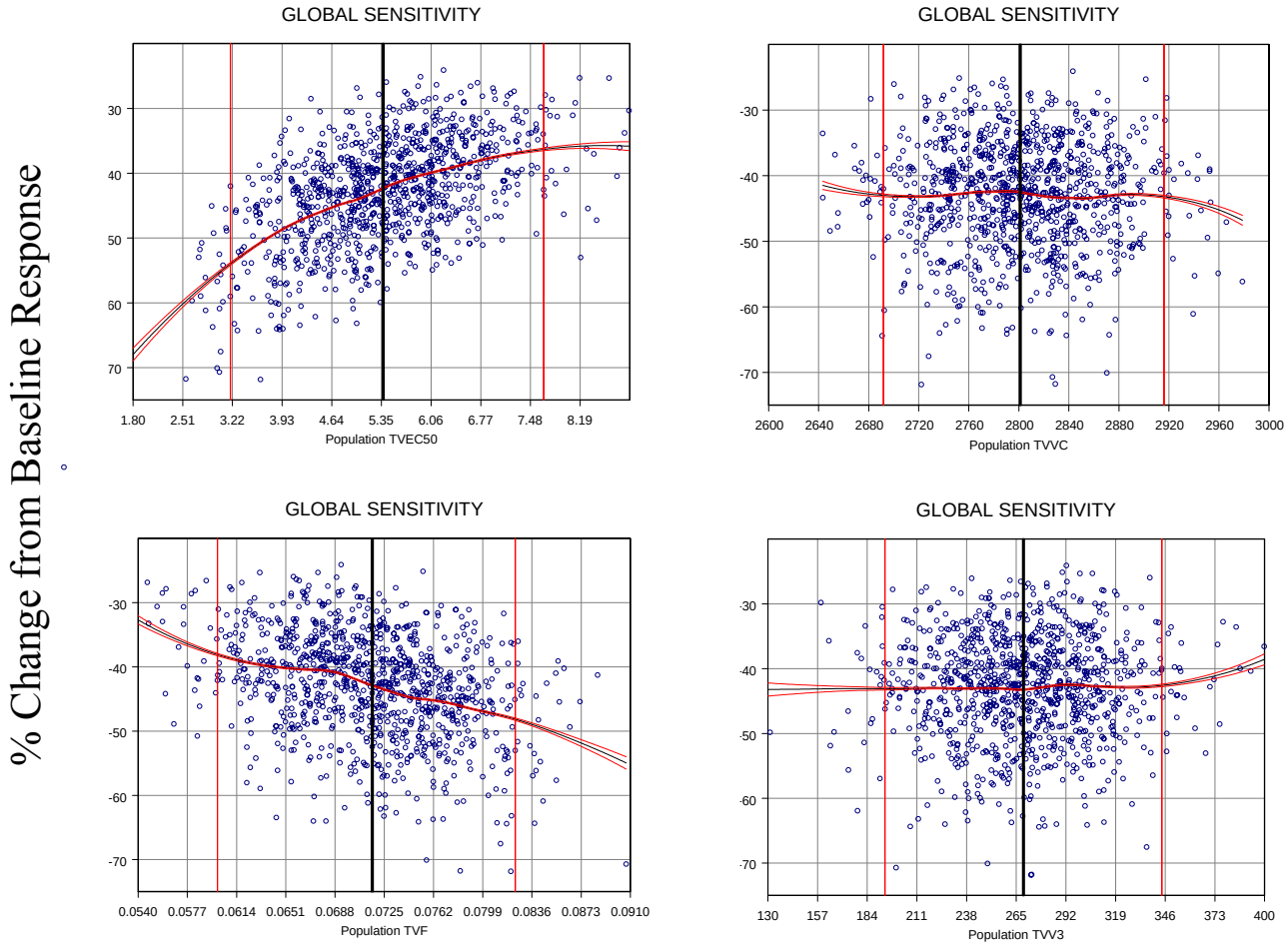
- Improved estimates of EMAX may significantly improve precision of the simulation predictions of trial outcomes

Example 3: View Population Variability and Uncertainty in Prediction For New Dose & Regimen



Competing therapy mean response at 2 weeks.

Sensitivity of Simulation Endpoint to Parameter Assumptions



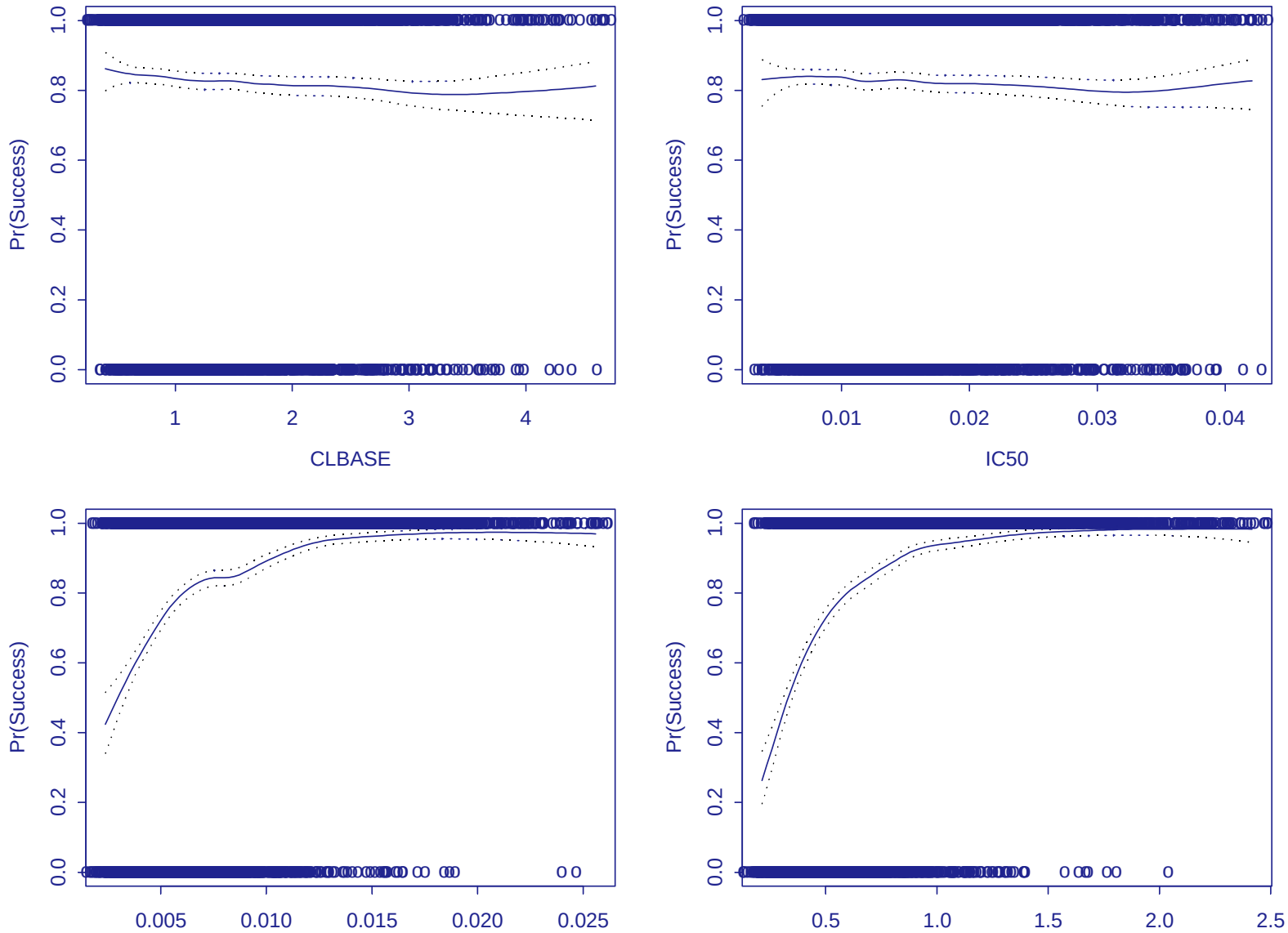
Example 4: Phase III Trial Simulation

Results of Local Sensitivity Analysis

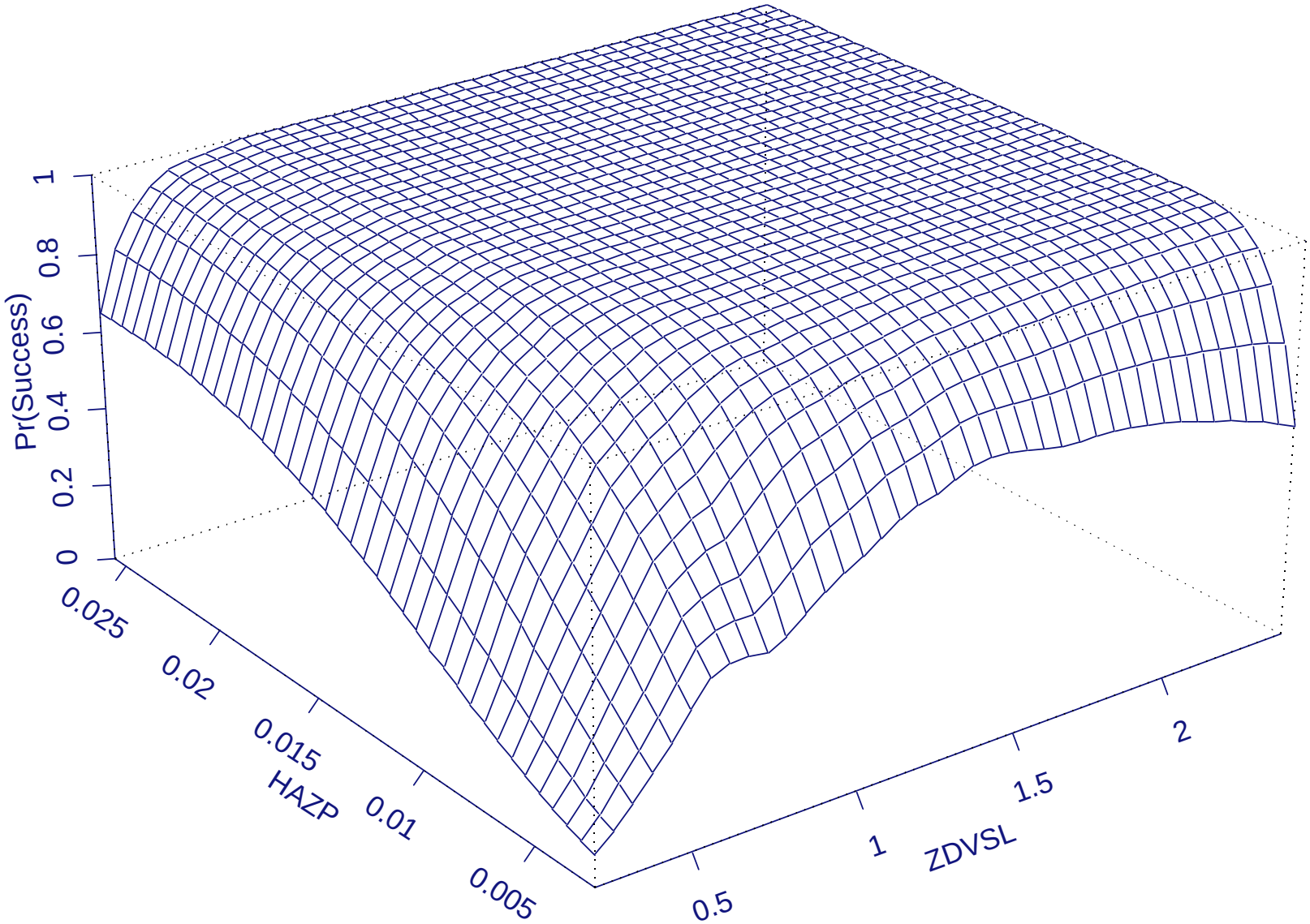
Fixed Value of ZDVSL	% Trials Successful[a]
0.25	30.6%
0.5	70.4%
0.735	93.0%
1.0	99.0%

[a]Results reflect 500 simulated trials of 2000 patients

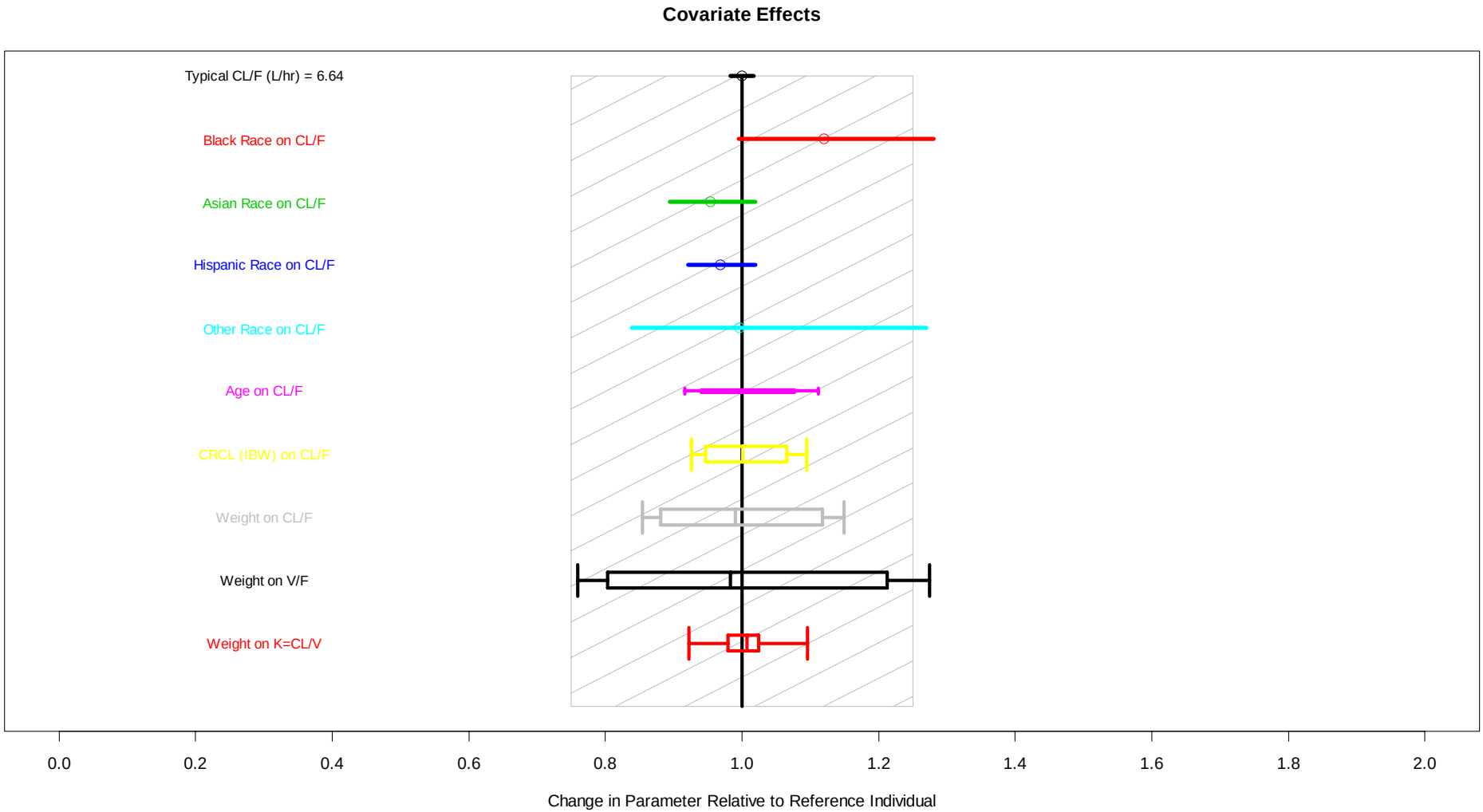
Global Sensitivity Analysis: Probability of Successful Trial vs. Uncertainty



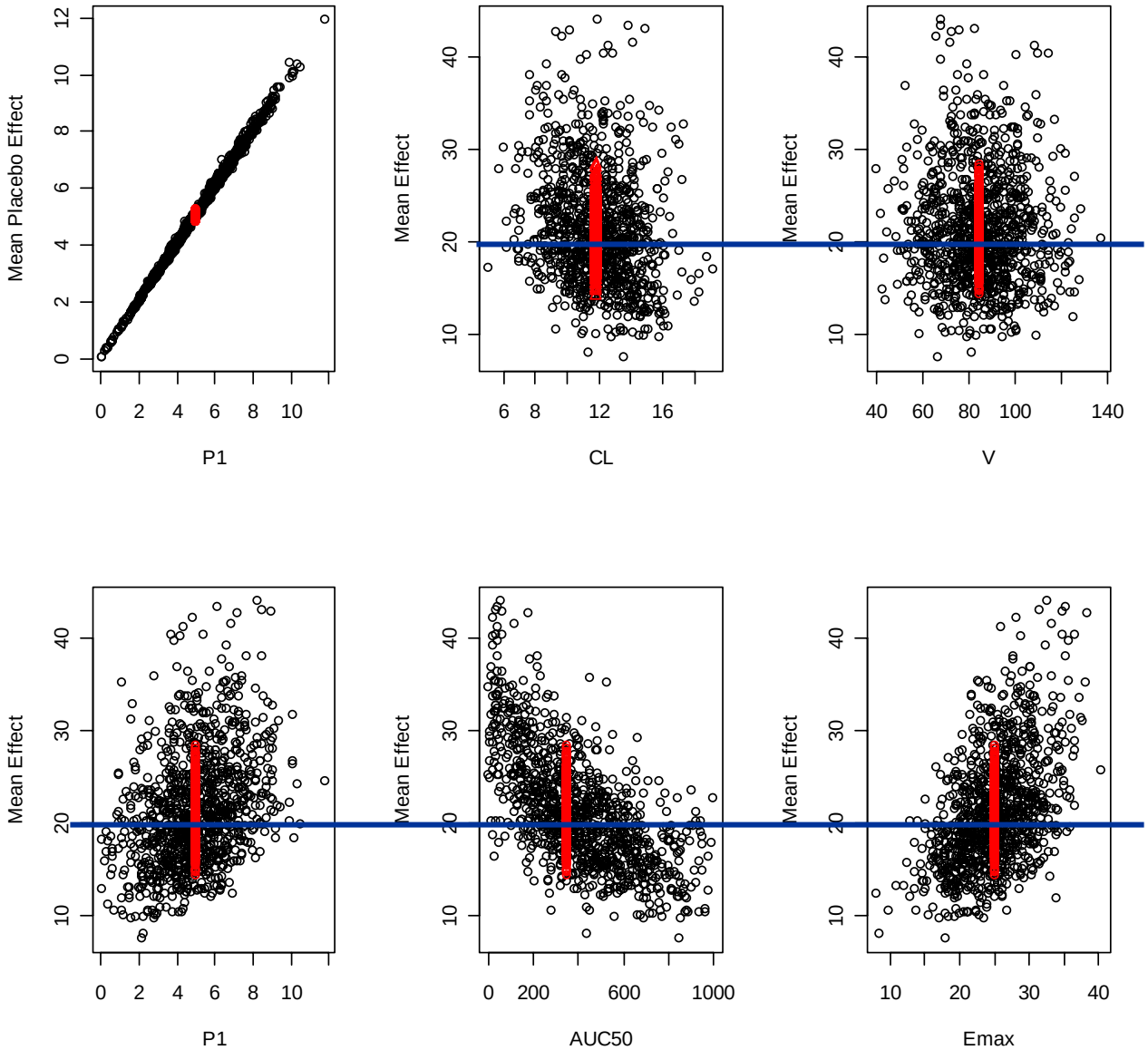
Sensitivity Analysis Surface: Most Influential Parameters



Example 5: Covariate Model for Population PK; Inferences in the Face of Uncertainty



Example 6: Mean Response Across Parameter Uncertainty



Summary of Examples

- Acknowledge Uncertainty:
  - Predictions of expected responses are viewed in the context of the uncertainty in the simulation parameters (and/or model)

- Impact on Model-Based Inferences:
  - Sensitivity analysis allows for quantitative description of outcome dependencies on model assumptions
  - This approach leads to an informed application of simulation results in the decision making process
  - Implementation requires specific tools but not more CPU-time intensive than simulations without uncertainty

How?

Simulation Plan

- Conventional CTS (without uncertainty):
  - Select model and model parameters
  - Simulate study 1000 times (with the same population parameters but different realizations of individual parameters)
  - Investigate range of possible outcomes (for fixed values of population parameters)
  - Repeat this process for different values of model parameters to investigate sensitivity of the results to assumptions (requires multiple repeats of simulations)

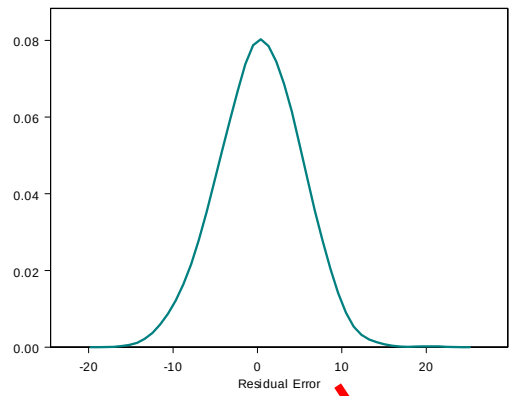
Simulation Plan

- CTS with uncertainty:
  - Select model and probability distribution of model / parameters (representing uncertainty)
  - Simulate study 1000 times (each time with different values of population parameters drawn from parameter distributions)
  - Investigate range of possible outcomes (given level of current knowledge)
  - Investigate sensitivity of the results to assumptions (does not require additional simulations)

Hierarchy of Random Variability & Uncertainty in Simulation

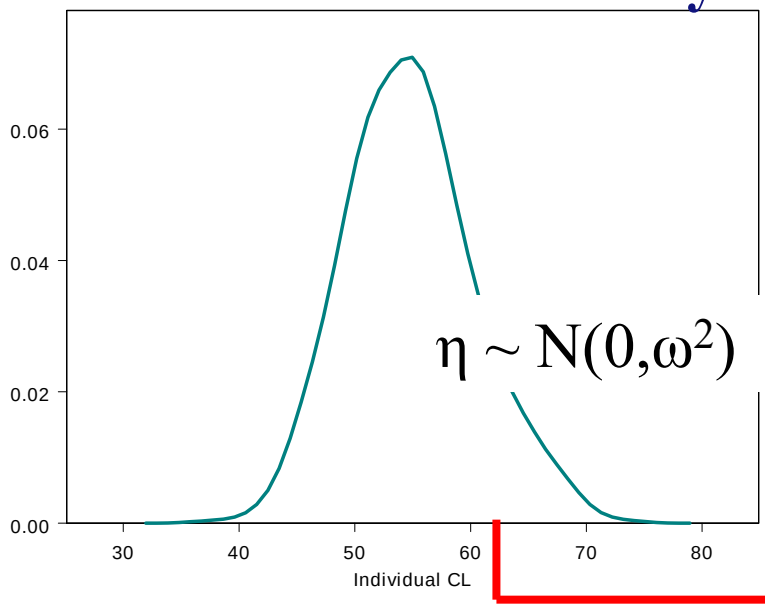
- Intra-individual, residual error (ε)
  - 1 draw from (0, σ^2) per observation, constant fixed-effect parameters (θ)
- Inter-individual error (η) in parameter
  - 1 draw from (0, ω^2) per individual, constant fixed-effect parameters (θ)
- Uncertainty in models and parameters
  - 1 draw from prior distribution for θ, Ω, Σ per trial

Residual Variability

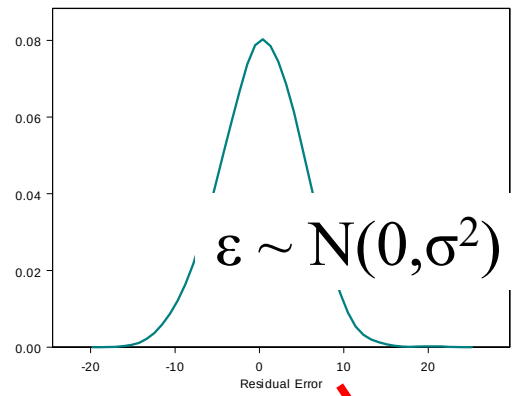


$$C_t = D/V*e^{-CLi/V*t} + \varepsilon_t$$

Interindividual Variability: CL



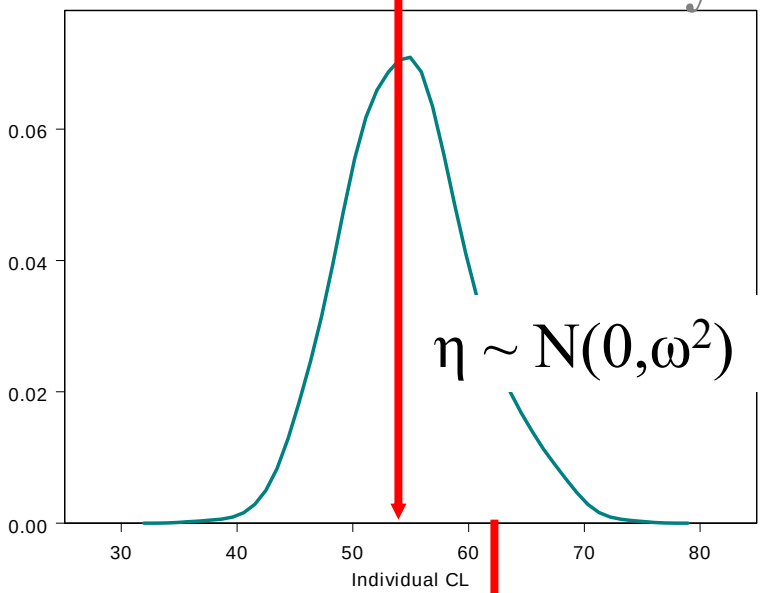
Residual Variability



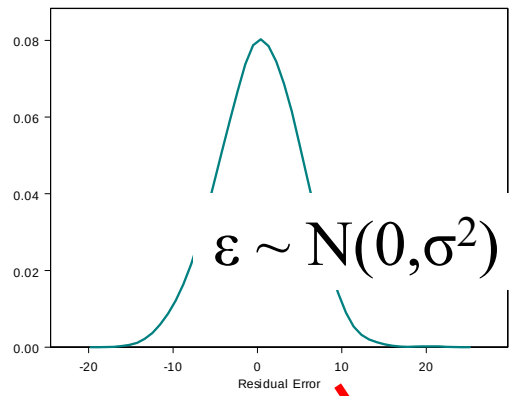
$$C_t = D/V * e^{-CLi/V * t} + \varepsilon_t$$

TVCL

Interindividual Variability: CL



Residual Variability

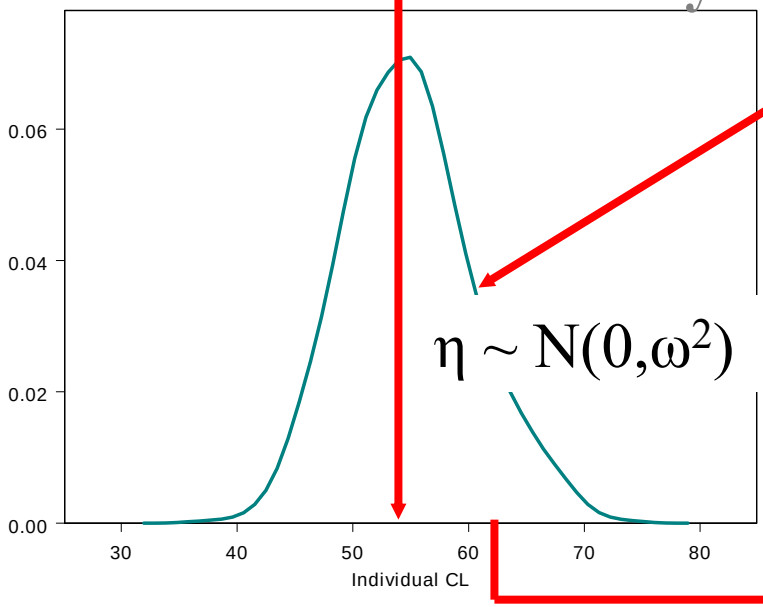


$$C_t = D/V*e^{-CLi/V*t} + \varepsilon_t$$

TVCL

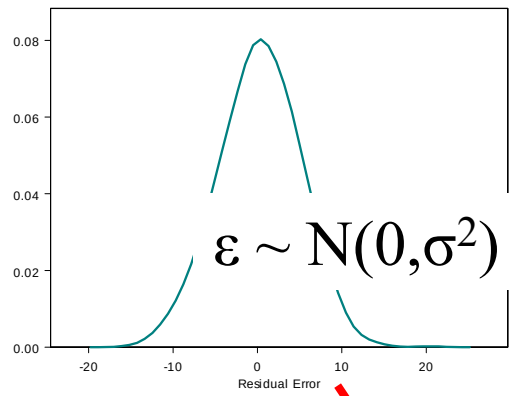
Population Variance in CL

Interindividual Variability: CL



$\eta \sim N(0,\omega^2)$

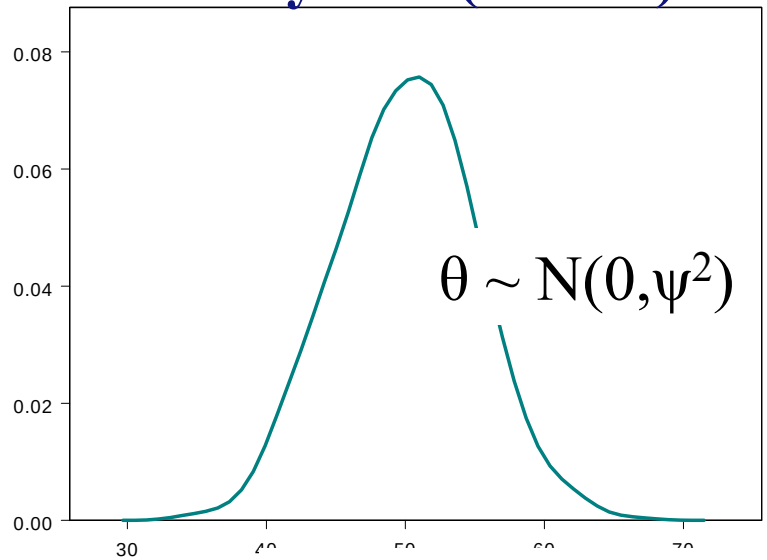
Residual Variability



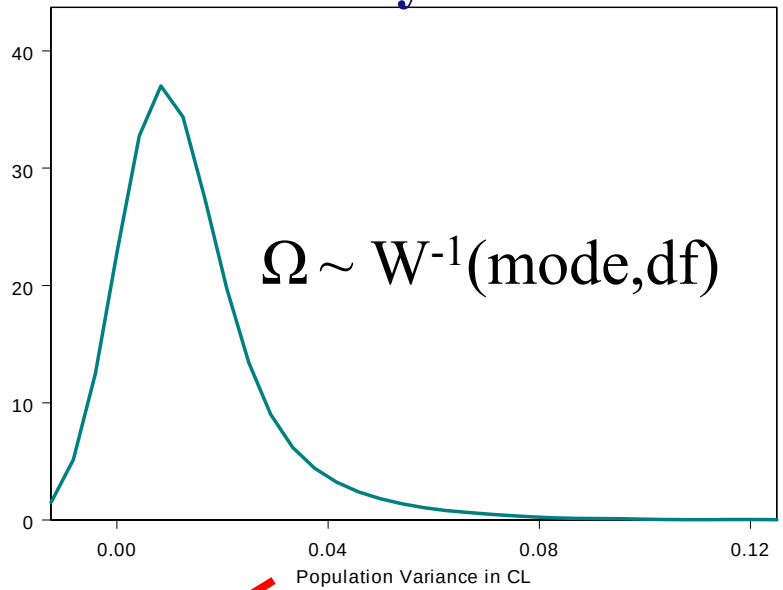
$\varepsilon \sim N(0,\sigma^2)$

$$C_t = D/V*e^{-CLi/V*t} + \varepsilon_t$$

Uncertainty in ln(TVCL)

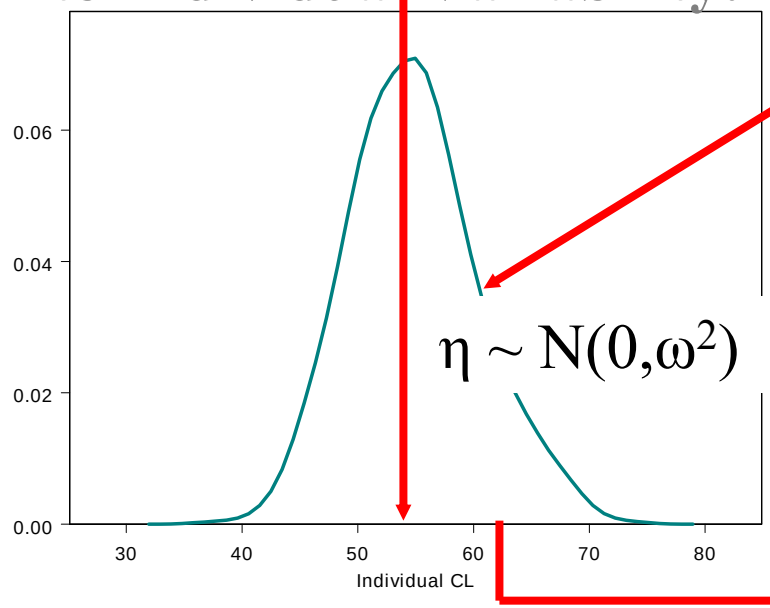


Uncertainty in Var CL

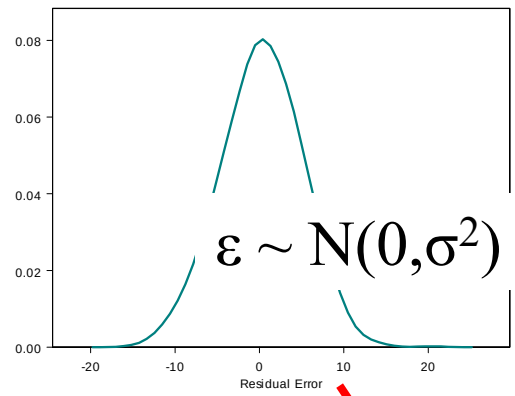


TVCL = exp(θ)

Interindividual Variability: CL



Residual Variability



$$C_t = D/V*e^{-CLi/V*t} + \varepsilon_t$$

Uncertainty in the Model (Competing Models)

- Through Uncertainty in Parameters:
  - Combinations of some parameters approximate a different model structure.
  - e.g. High EC50 approximates linear model

- Simulate from Expected Probability of Each Model:

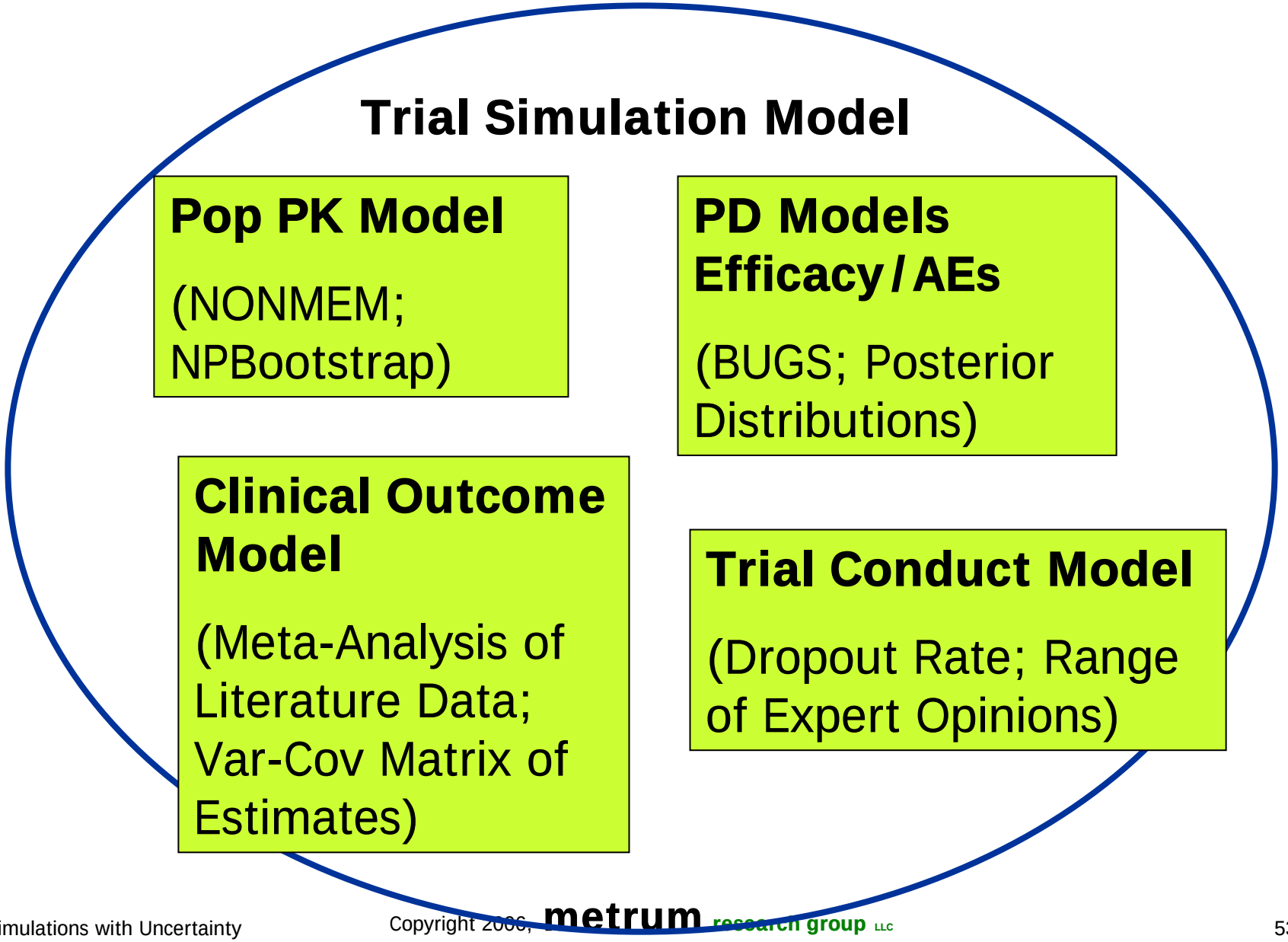
  P(Model A) = 0.7 P(Model B) = 0.3

  - Draw random uniform variable (0-1), R
  - Model A if R <= 0.7; Model B if R > 0.7

Obtaining Measures of Uncertainty

- Results from prior modeling exercise
  - Variance-covariance matrix of estimates
  - Bootstrap parameter distributions
  - Bayesian posterior distributions
- Review of literature for ranges of plausible values
- Poll experts (everyone's view can be part of the simulation)

Assembling Simulation Model Components



Simulation Tool: Requirements

1. Monte Carlo simulation hierarchy with multiple levels of nested random effects (at least 3)
2. Ability to incorporate joint uncertainty distributions from other methods (e.g. bootstrap, Bayesian)
3. Simulation and estimation (ML) for typical population PK and PD systems in same tool
4. Programmable/extensible language with data manipulation and graphics capability
5. Platform neutral (Win, Unix, Linux, Mac OS X)

Current Simulation Tools

Some programs with Monte Carlo simulation capabilities at parameter uncertainty level are available, but not all requirements are met:

- WinBugs
- NONMEM PRIOR subroutine
- Trial Simulator
- Others...

NMSUDs R/NONMEM Package

1. Generates draws from the uncertainty distributions at inter-trial level, maintaining joint distribution (covariance) of parameters

-OR-

1. Samples from previously determined uncertainty distributions (e.g. Bootstrap, Bayesian Posteriors)
2. Generates NONMEM control streams for simulation (estimation)
3. Runs NONMEM or R for simulation (and possibly estimation) of each trial
4. Summarizes the results of each trial and across all trials

Parameter type (NONMEM name)	Distribution	Parameters of the distribution	Implementation	How to assign distribution parameters based on NONMEM run
Single uncorrelated population parameter (THETA)	Normal	Mean μ, variance σ^2	Standard R function rnorm(., μ, σ)	μ: population parameter estimate; σ: standard error of the parameter estimate.
Set of correlated population parameters (THETA)	Multivariat Normal	Vector of mean values M, variance-covariance matrix Σ	Standard R function mvrnorm(., M, Σ)	M: vector of population parameter estimate; Σ: variance-covariance matrix of the parameter estimates.
Variance of the random effect (OMEGA)	Scaled Inverse χ^2	Number of degrees of freedom ν, scale s^2.	Standard R function νs^2/rchisq(., ν)	ν: number of patients used to obtain the estimate; s^2: estimated variance of the random effect.
Variance-covariance matrix of the random effects (OMEGA)	Inverse Wishart	Number of degrees of freedom ν, scale matrix S. Implicit parameter is the S matrix dimension k.	Proprietary R function myriwish(k, ν, νS) based on the standard riwish() function	ν: number of patients used to obtain the estimate; νS: estimated variance-covariance matrix of the random effect.
Variance of the error term (SIGMA)	Scaled Inverse χ^2	Number of degrees of freedom ν, scale s^2.	Standard R function νs^2/rchisq(., ν)	ν: number between the number of patients and the number of observations used to obtain the estimate; s^2: estimated variance of the error.

Sample from Uncertainty Distributions

C:\code\NMSUDSalpha1\Scripts\Example2Apr2006.R - R Editor

```
SourceDirName <- "c:/code/NMSUDSalpha1/Scripts/"
DirName <- "c:/code/NMSUDSalpha1/Example2/"
FigureDir <- DirName
source(paste(SourceDirName,"SimulationFromFileJan30.R",sep=""))
source(paste(SourceDirName,"CreateParametersOct24.R",sep=""))
source(paste(SourceDirName,"PostProcessingOct28.R",sep=""))

ThetaMean  <-c(100,1000,7500,500,0.5,1,500)
ThetaCovar <- diag(c(150,15000,1000000,6400,0.1,0.04,15000))
OmegaModeList <-list(0.04,0.09,1,0.09,0.25)
OmegaDfList <-c(50,50,50,50,50)
SigmaModeList <- list(0.04,0.04)
SigmaDfList <- c(75,75)

# this part ensures reproducability:
set.seed(123)
rnorm(5)
# -0.56047565 -0.23017749  1.55870831  0.07050839  0.12928774

NsimPar <- 14
nsim <- 100
parameters <- CreateParametersForSimulation(nsim=1.5*nsim,
               ThetaMean=ThetaMean,ThetaCovar=ThetaCovar,
               OmegaModeList=OmegaModeList,OmegaDfList=OmegaDfList,
               SigmaModeList=SigmaModeList,SigmaDfList=SigmaDfList)

bounds <- data.frame(par =1:NsimPar,lower =rep(0,NsimPar),upper=rep(Inf,NsimPar))
parametersTruncated <- TruncateParametersForSimulation(parameters, bounds)
parametersTruncated <- parametersTruncated[1:nsim,]
write.table(parametersTruncated, file=paste(DirName,"Example2Par.csv",sep=""),
                          quote = F,sep=",",row.names = F,col.names = F)
```

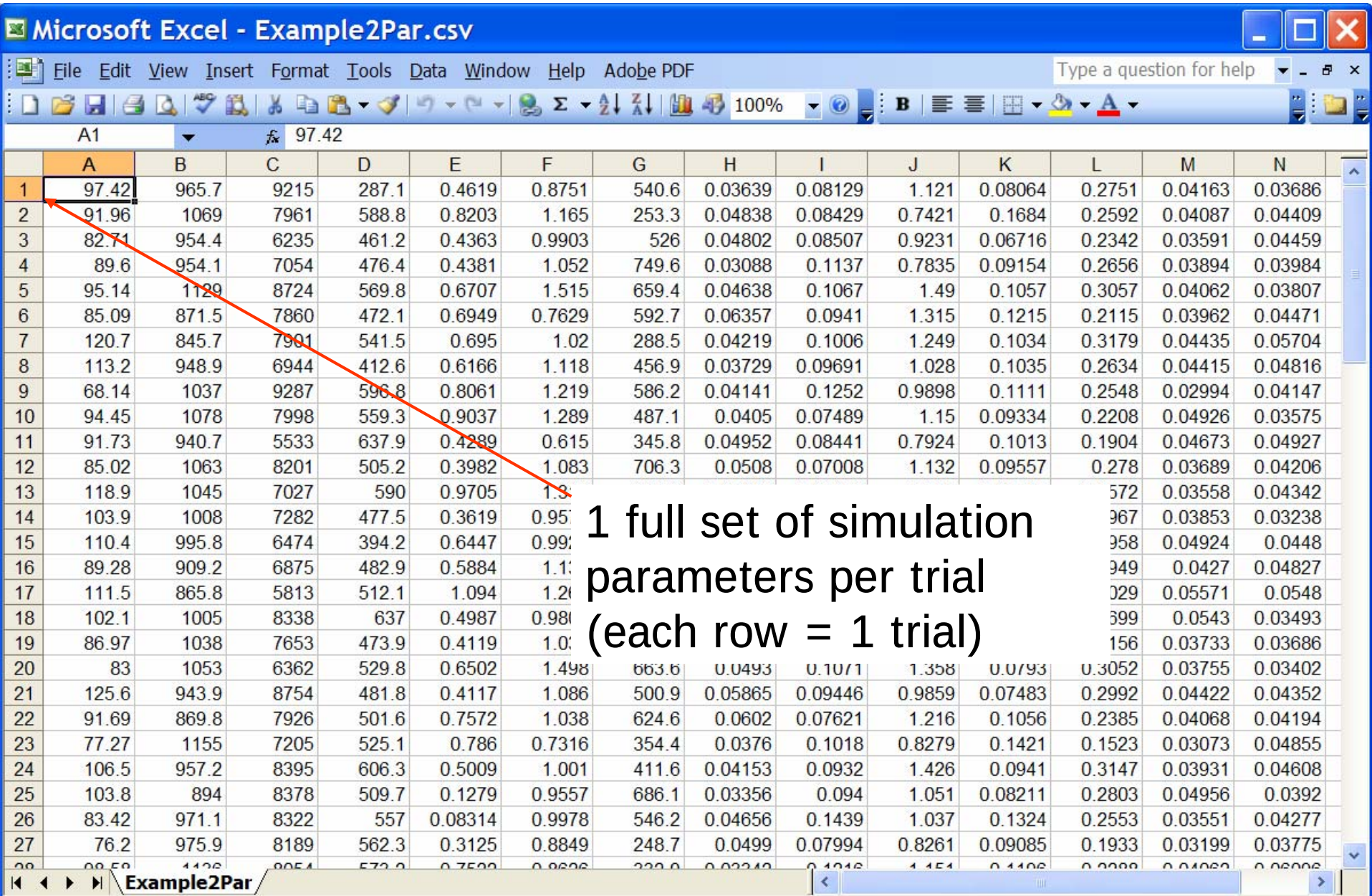
Sample from Uncertainty Distributions

RGui - [C:\code\NMSUDSalpha1\Scripts\Example1Apr2006.R - R Editor]

File Edit Packages Windows Help

```
SourceDirName <- "c:/code/NMSUDSalpha1/Scripts/"
DirName <- "c:/code/NMSUDSalpha1/Example1/"
source(paste(SourceDirName,"SimulationFromFileApr2006.R",sep=""))
source(paste(SourceDirName,"CreateParametersApr2006.R",sep=""))
source(paste(SourceDirName,"PostProcessingOct28.R",sep=""))


ThetaMean  <-c(11.8,85)
ThetaCovar <- matrix(c(0.232,0.449,0.449,12.8),2,2)
OmegaModeList <-matrix(c(0.0572,0.011,0.011,0.0615),2,2)
OmegaDfList <-20
SigmaModeList <- 0.0454
SigmaDfList <- 200

# this part ensures reproducability:
set.seed(123)
rnorm(5)
# -0.56047565 -0.23017749  1.55870831  0.07050839  0.12928774


parameters <- CreateParametersForSimulation(nsim=100,
               ThetaMean=ThetaMean,ThetaCovar=ThetaCovar,
               OmegaModeList=OmegaModeList,OmegaDfList=OmegaDfList,
               SigmaModeList=SigmaModeList,SigmaDfList=SigmaDfList)

bounds <- data.frame(par =c(1,2),lower =c(5,30),upper=c(20,150))
parametersTruncated <- TruncateParametersForSimulation(parameters, bounds)
write.table(parametersTruncated, file=paste(DirName,"Example1Par.csv",sep=""),
                          quote = F,sep=",",row.names = F,col.names = F)
```

Parameters Generated from Uncertainty Distributions (or Bootstrap, Bayesian Posteriors, etc.)



	A	B	C	D	E	F	G	H	I	J	K	L	M	N
1	97.42	965.7	9215	287.1	0.4619	0.8751	540.6	0.03639	0.08129	1.121	0.08064	0.2751	0.04163	0.03686
2	91.96	1069	7961	588.8	0.8203	1.165	253.3	0.04838	0.08429	0.7421	0.1684	0.2592	0.04087	0.04409
3	82.71	954.4	6235	461.2	0.4363	0.9903	526	0.04802	0.08507	0.9231	0.06716	0.2342	0.03591	0.04459
4	89.6	954.1	7054	476.4	0.4381	1.052	749.6	0.03088	0.1137	0.7835	0.09154	0.2656	0.03894	0.03984
5	95.14	1129	8724	569.8	0.6707	1.515	659.4	0.04638	0.1067	1.49	0.1057	0.3057	0.04062	0.03807
6	85.09	871.5	7860	472.1	0.6949	0.7629	592.7	0.06357	0.0941	1.315	0.1215	0.2115	0.03962	0.04471
7	120.7	845.7	7901	541.5	0.695	1.02	288.5	0.04219	0.1006	1.249	0.1034	0.3179	0.04435	0.05704
8	113.2	948.9	6944	412.6	0.6166	1.118	456.9	0.03729	0.09691	1.028	0.1035	0.2634	0.04415	0.04816
9	68.14	1037	9287	596.8	0.8061	1.219	586.2	0.04141	0.1252	0.9898	0.1111	0.2548	0.02994	0.04147
10	94.45	1078	7998	559.3	0.9037	1.289	487.1	0.0405	0.07489	1.15	0.09334	0.2208	0.04926	0.03575
11	91.73	940.7	5533	637.9	0.4289	0.615	345.8	0.04952	0.08441	0.7924	0.1013	0.1904	0.04673	0.04927
12	85.02	1063	8201	505.2	0.3982	1.083	706.3	0.0508	0.07008	1.132	0.09557	0.278	0.03689	0.04206
13	118.9	1045	7027	590	0.9705	1.3						572	0.03558	0.04342
14	103.9	1008	7282	477.5	0.3619	0.95						967	0.03853	0.03238
15	110.4	995.8	6474	394.2	0.6447	0.99						958	0.04924	0.0448
16	89.28	909.2	6875	482.9	0.5884	1.1						949	0.0427	0.04827
17	111.5	865.8	5813	512.1	1.094	1.2						029	0.05571	0.0548
18	102.1	1005	8338	637	0.4987	0.98						599	0.0543	0.03493
19	86.97	1038	7653	473.9	0.4119	1.0						156	0.03733	0.03686
20	83	1053	6362	529.8	0.6502	1.498	663.6	0.0493	0.1071	1.358	0.0793	0.3052	0.03755	0.03402
21	125.6	943.9	8754	481.8	0.4117	1.086	500.9	0.05865	0.09446	0.9859	0.07483	0.2992	0.04422	0.04352
22	91.69	869.8	7926	501.6	0.7572	1.038	624.6	0.0602	0.07621	1.216	0.1056	0.2385	0.04068	0.04194
23	77.27	1155	7205	525.1	0.786	0.7316	354.4	0.0376	0.1018	0.8279	0.1421	0.1523	0.03073	0.04855
24	106.5	957.2	8395	606.3	0.5009	1.001	411.6	0.04153	0.0932	1.426	0.0941	0.3147	0.03931	0.04608
25	103.8	894	8378	509.7	0.1279	0.9557	686.1	0.03356	0.094	1.051	0.08211	0.2803	0.04956	0.0392
26	83.42	971.1	8322	557	0.08314	0.9978	546.2	0.04656	0.1439	1.037	0.1324	0.2553	0.03551	0.04277
27	76.2	975.9	8189	562.3	0.3125	0.8849	248.7	0.0499	0.07994	0.8261	0.09085	0.1933	0.03199	0.03775

Typical NONMEM $SIM Control Stream

```
$PROB RUN# 001
$INPUT C ID AMT TIME EVID DV WT SS II
$DATA ../Example2Data.csv IGNORE=@
$SUBROUTINE ADVAN4 TRAN4
$PK
   TVCL = THETA(1)*(WT/70)**0.75
   TVV2 = THETA(2)*WT/70
   V3   = THETA(3)*WT/70
   Q    = THETA(4)*(WT/70)**0.75
   CL   = TVCL*EXP(ETA(1))
   V2   = TVV2*EXP(ETA(2))
   F1   = 2
   S2   = V2/1000
   T1  = TVCL/TVV2
   T23 = Q/TVV2
   T32 = Q/V3
   TL1  = ((T1+T23+T32)+SQRT((T1+T23+T32)**2-4*T1*T32))/2
   TVKA = THETA(5)+TL1
   KA   = TVKA*EXP(ETA(3))
   EMAX = THETA(6)*EXP(ETA(4))
   EC50 = THETA(7)*EXP(ETA(5))
$ERROR
   CONC=A(2)/S2
   EFF = EMAX*CONC/(EC50+CONC)
   Y=EFF*EXP(EPS(1))
   IPRED=CONC*EXP(EPS(2))
```

```
$THETA
100      ; 1 TVCL
1000     ; 2 TVV2
7500     ; 3 TVV3
500      ; 4 TVQ
0.5      ; 5 TVKA
1        ; 6 EMAX
500      ; 7 EC50
$OMEGA
0.04     ; 1 CL
0.09     ; 2 V2
1.00     ; 3 KA
0.09     ; 4 EMAX
0.25     ; 5 EC50
$SIGMA
0.01     ; 1 EFF
0.04     ; 2 PK
$SIMULATION (12345) (6789 UNIFORM)
$TABLE EVID TIME CONC IPRED EFF DV NOPRINT NOHEADER
       NOAPPEND FILE=../001.tab
```

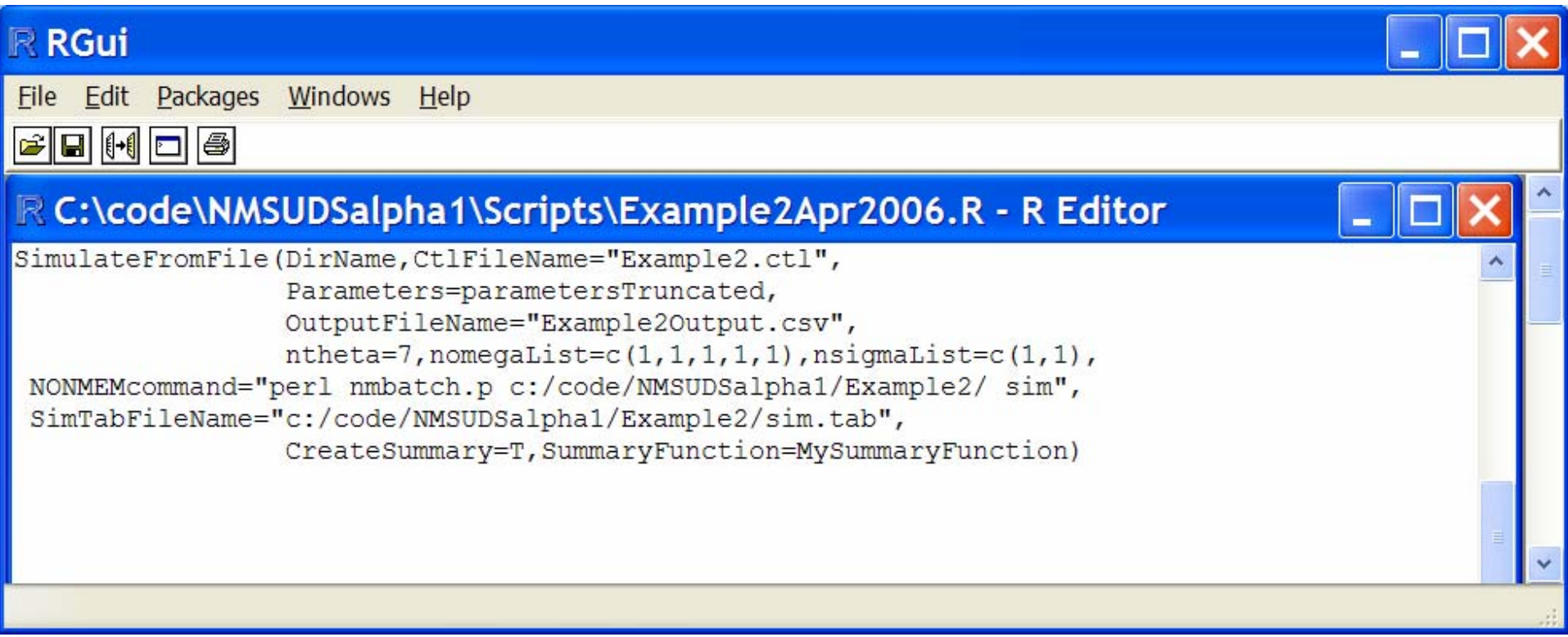
Constraining Simulated Parameters

- When simulating from a multi-variate Normal covariance matrix, use caution about plausible values for population-level parameters.
- Constrain model so that plausible values are simulated, e.g.:

```
LNCL=THETA
CL=EXP(LNCL)
```

- Bootstrap distributions and Bayesian posteriors may already be constrained to plausible values

Simulate from Uncertainty Distributions using NONMEM Model Control Stream



NMSUDs R/NONMEM Package

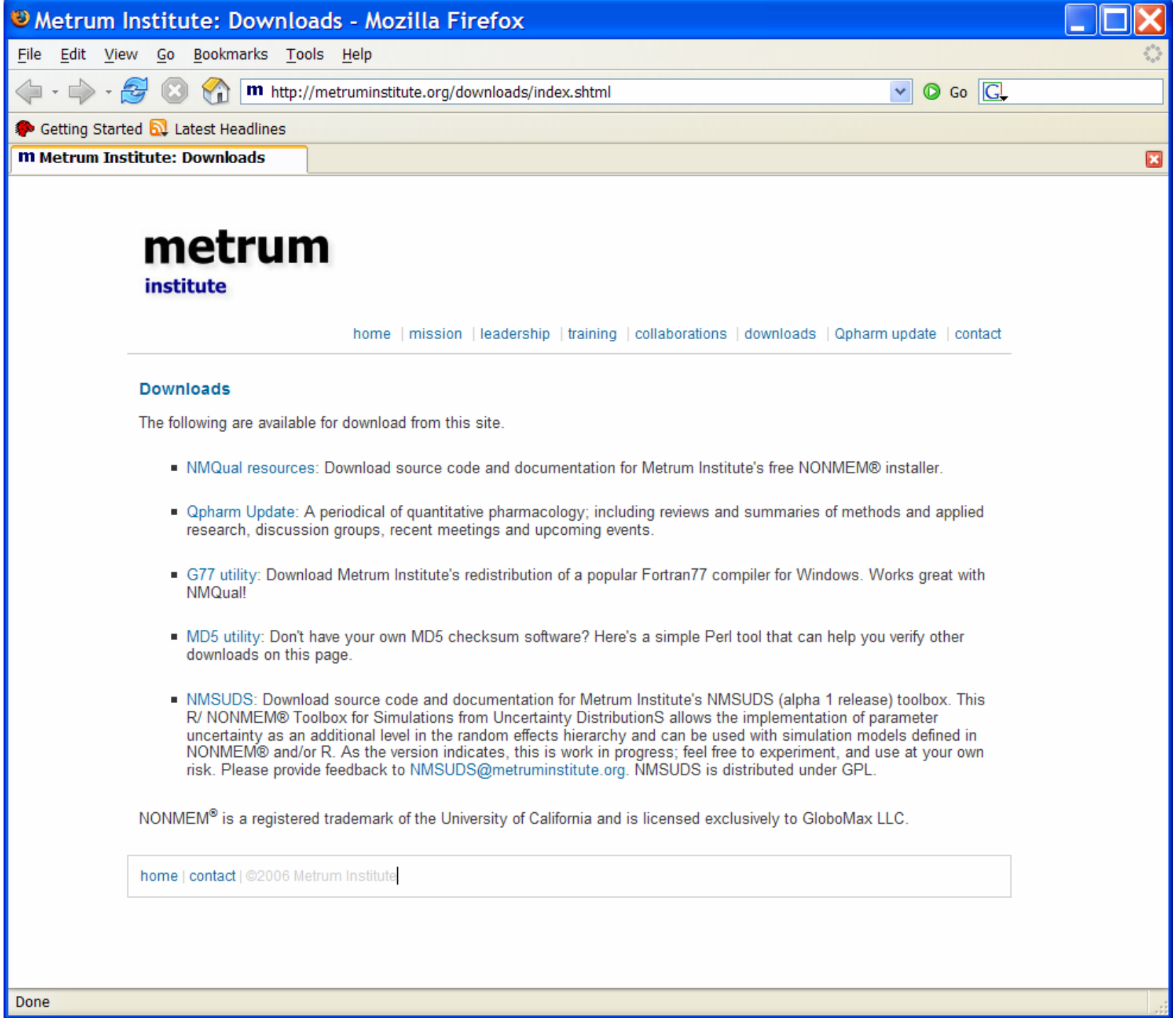
Open-source tool, distributed under GPL.

Download alpha version of code from:

www.metruminstitute.org/downloads

Forward questions/comments to:

NMSUDs@metruminstitute.org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Acknowledgements

- Metrum Research Group Scientific Team
- John Mondick, Jeff Barrett (The Children's Hospital of Philadelphia)
- Industry collaborators (examples)

Questions or Comments?