

NMSUDs: R / NONMEM® Toolbox for Simulations from Uncertainty Distributions

MUFPADA

May 2 & 3, 2006

Ann Arbor, MI

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Overview

Acknowledging uncertainty in simulation parameters/models:

- Why?
 - Value of the approach
 - Some examples
- How?
 - Methods
 - 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.

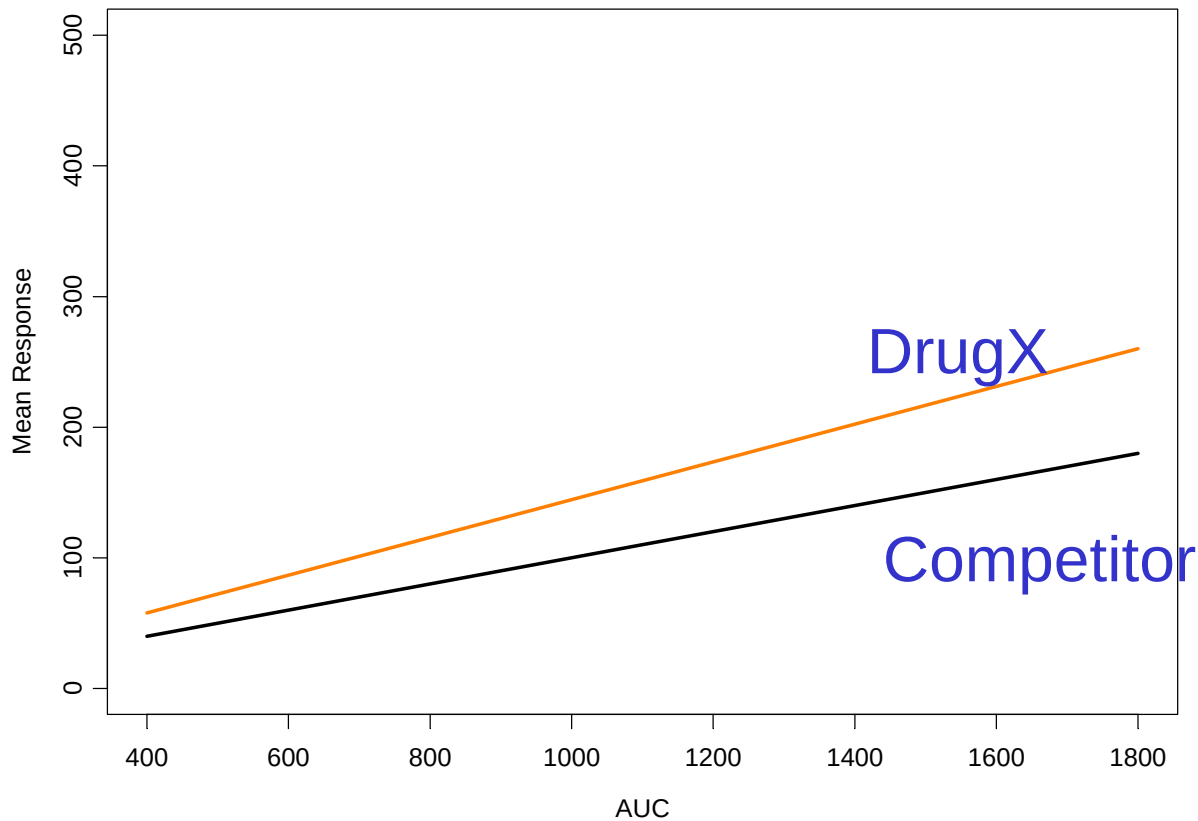
Why Include Uncertainty in M&S?

- When uncertainty is not included, simulation results are only valid if the model and parameters are true.
- 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

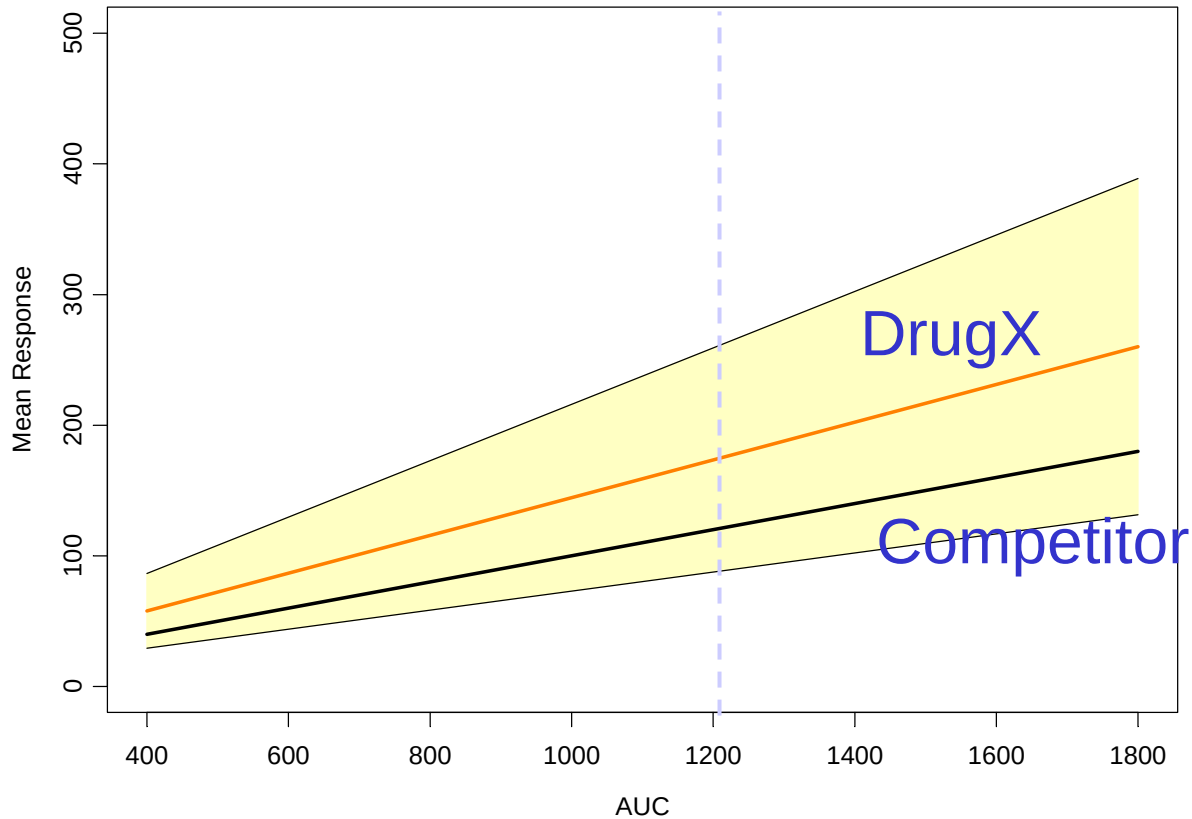
Simulation vs. Competitor

(simulation without uncertainty)

What is the probability that DrugX response > Competitor?

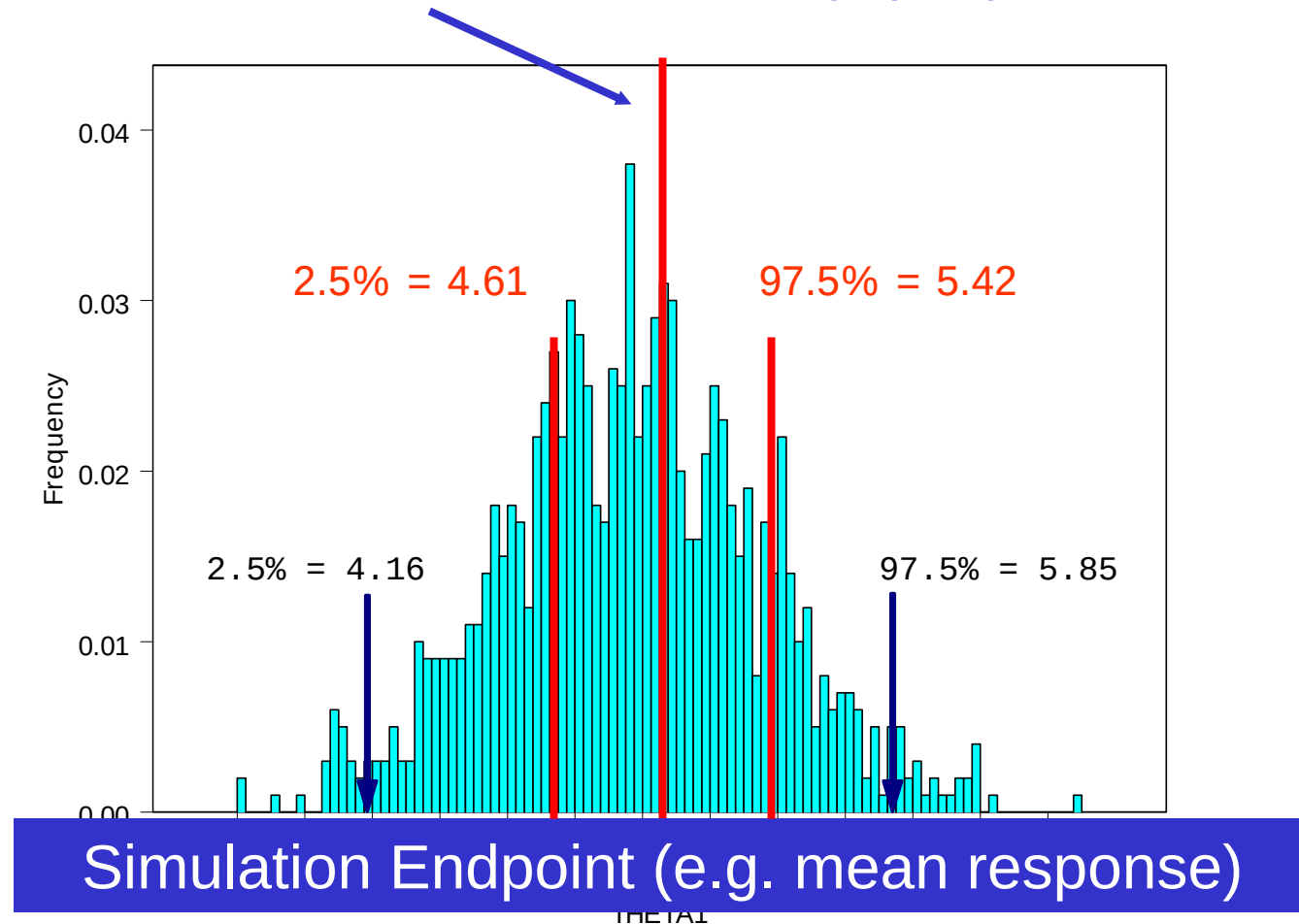


Exposure-Response Simulation (with uncertainty in DrugX response)



Simulation with Uncertainty Results

simulation without uncertainty (red)

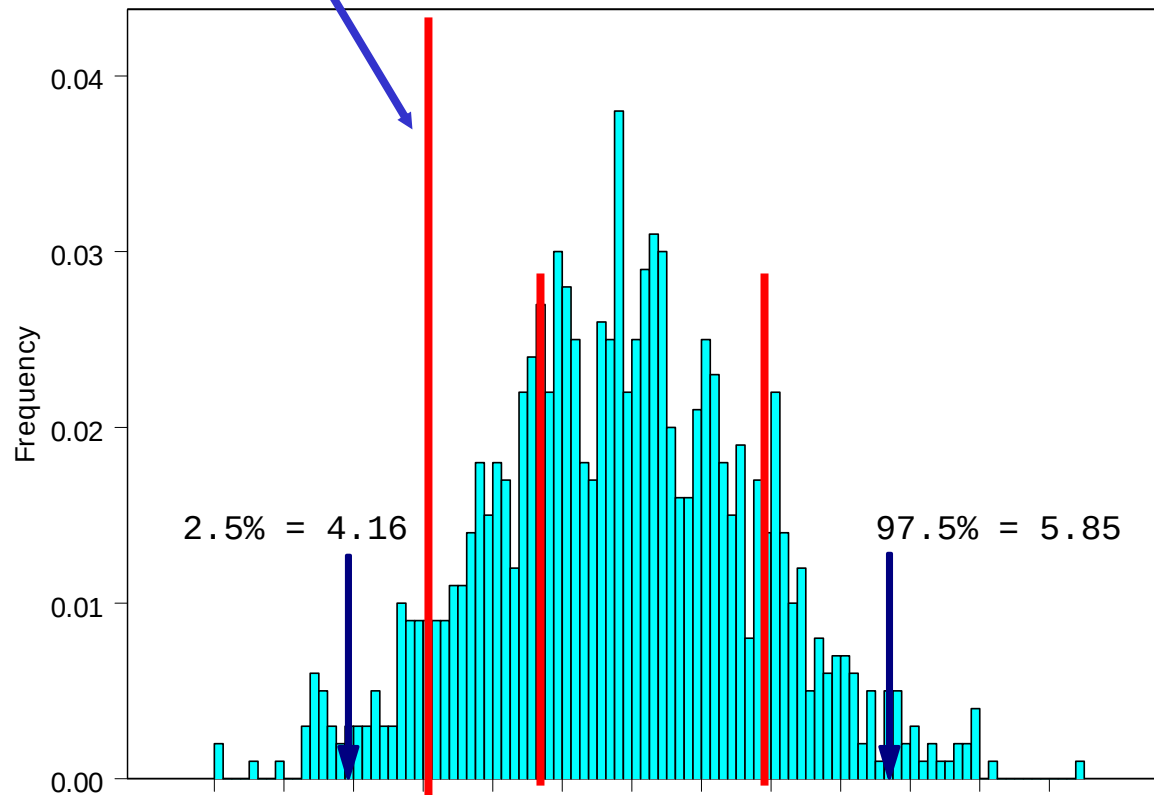


Simulation with Uncertainty Results

Probability that mean response > reference:

No uncertainty: 100%; With uncertainty: 94%

reference response



Simulation Endpoint (e.g. mean response)

Example 1: Optimal Design of the Trial Using Simulations with Uncertainty

Implemented by John Mondick
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

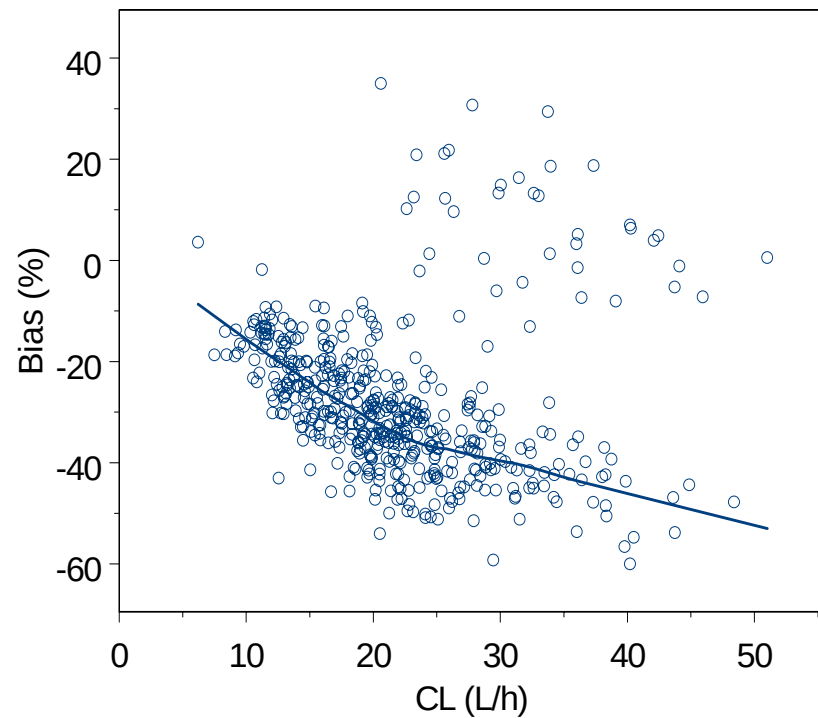
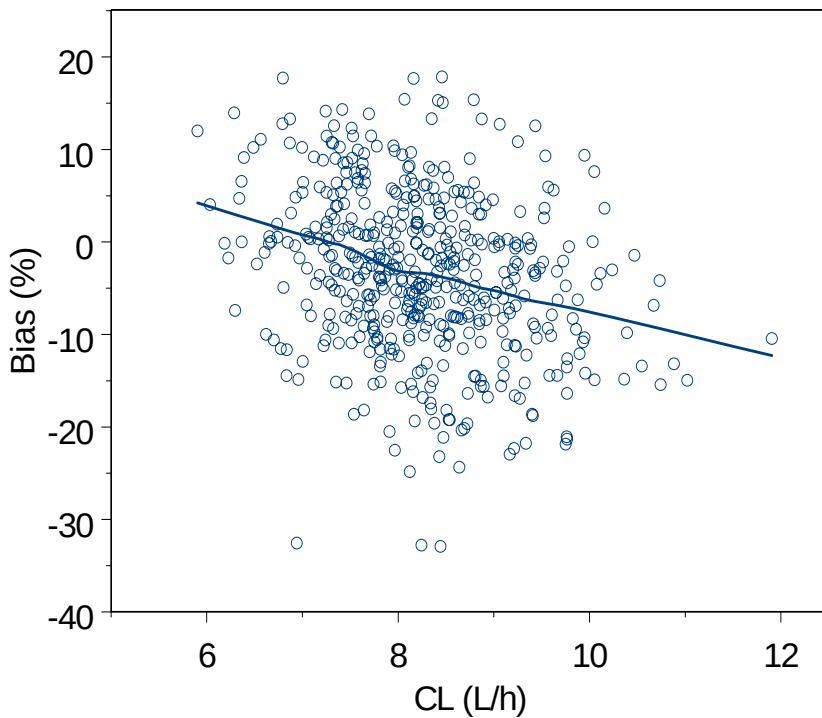
Initial Study Design

- $n=200$
- 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 Results: CL

Drug 1

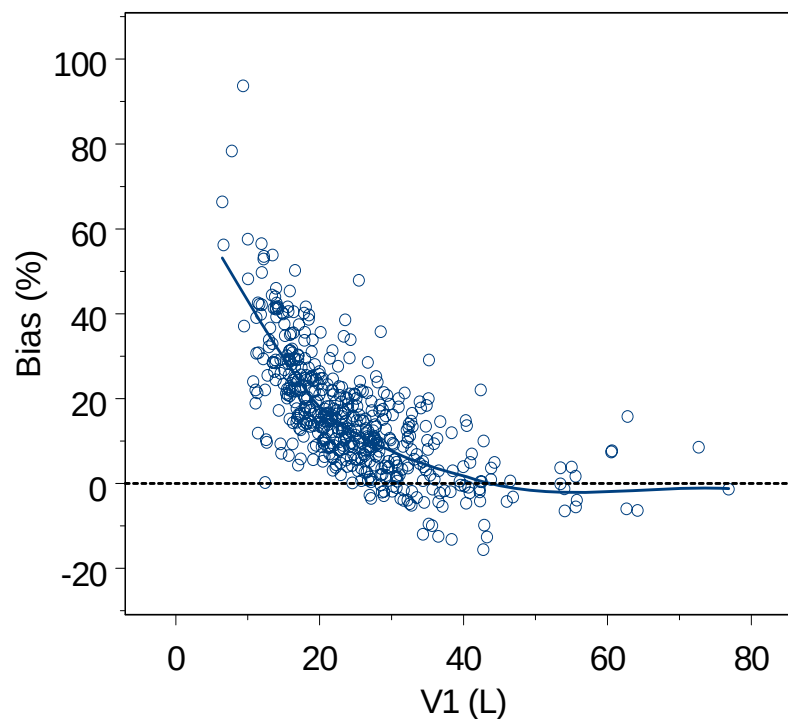
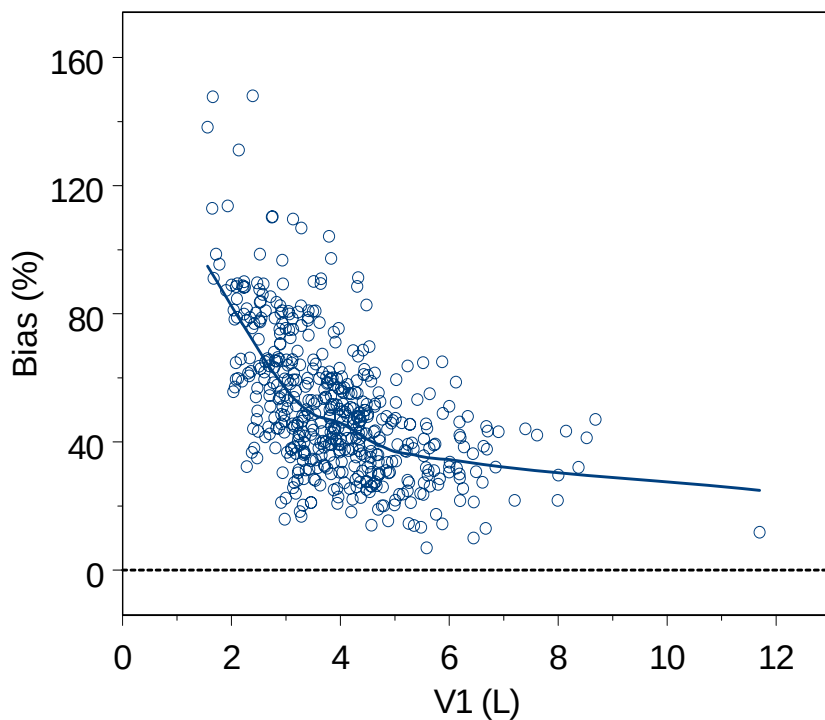
Drug 2



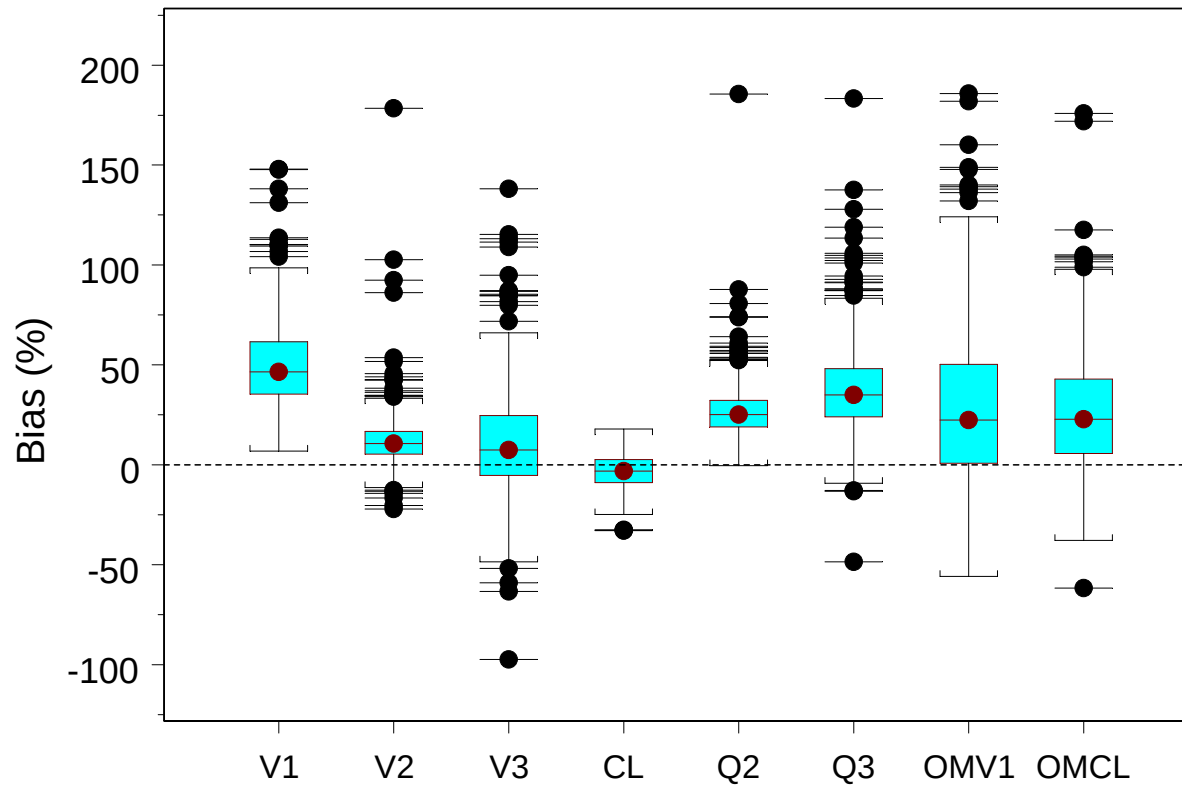
Initial Design Results: V

Drug 1

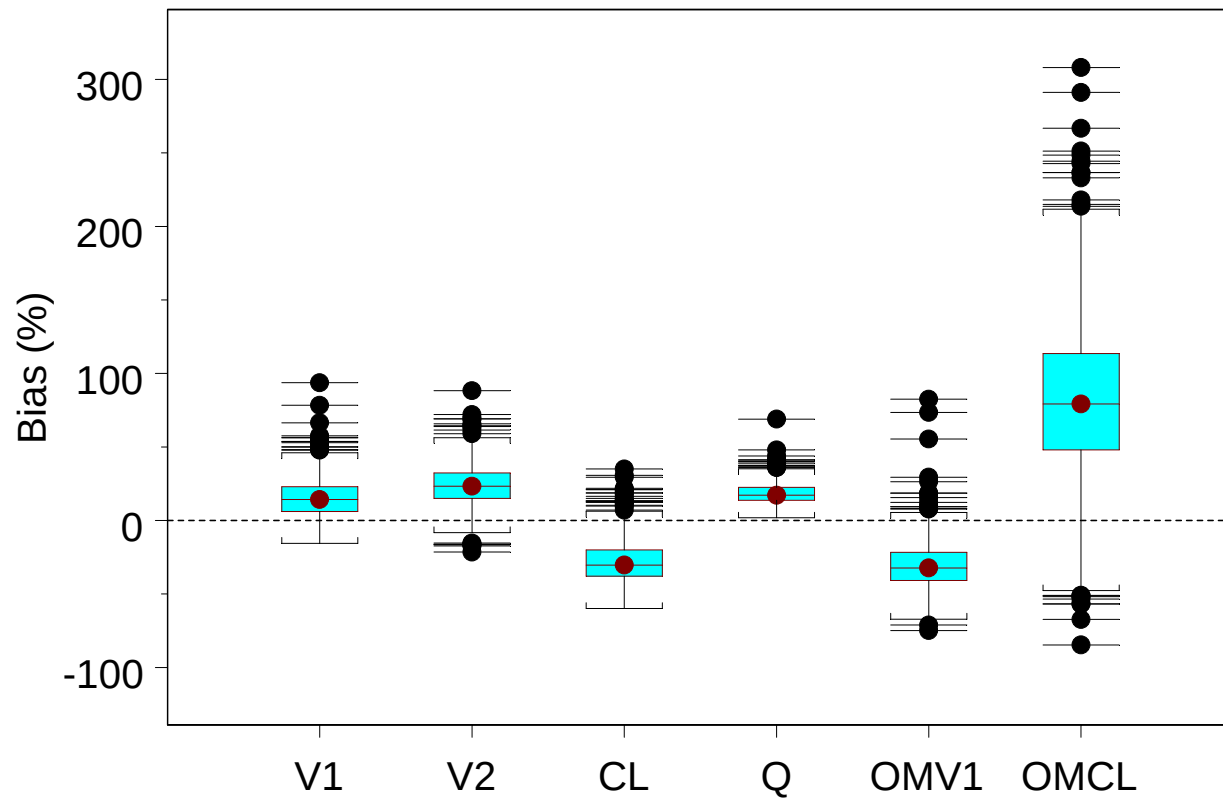
Drug 2



Initial Design Results: Drug 1 Bias



Initial Design Results: Drug 2 Bias



What to do?

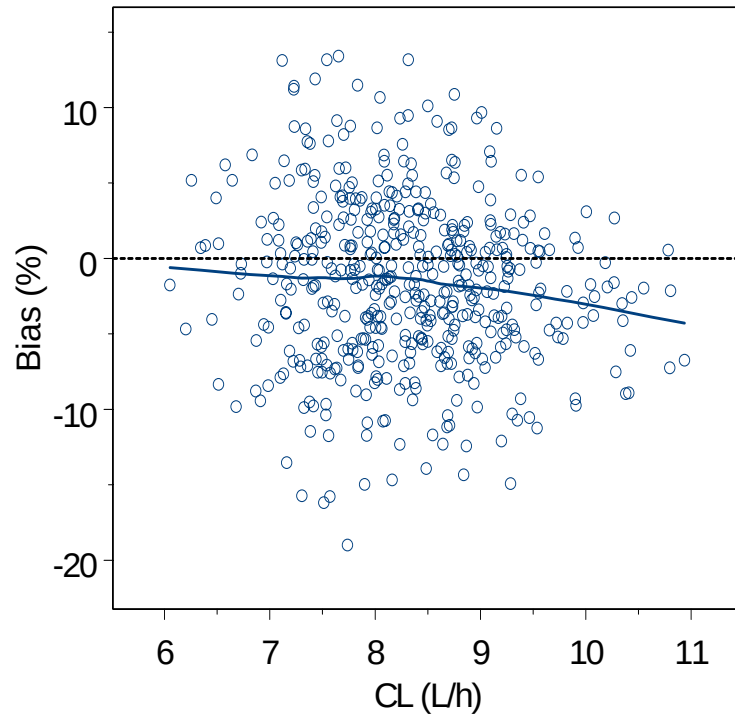
- Improve our knowledge about population parameters (reduce uncertainty)
- Improve design to make it robust to the assumptions about the model parameters

Final Study Design

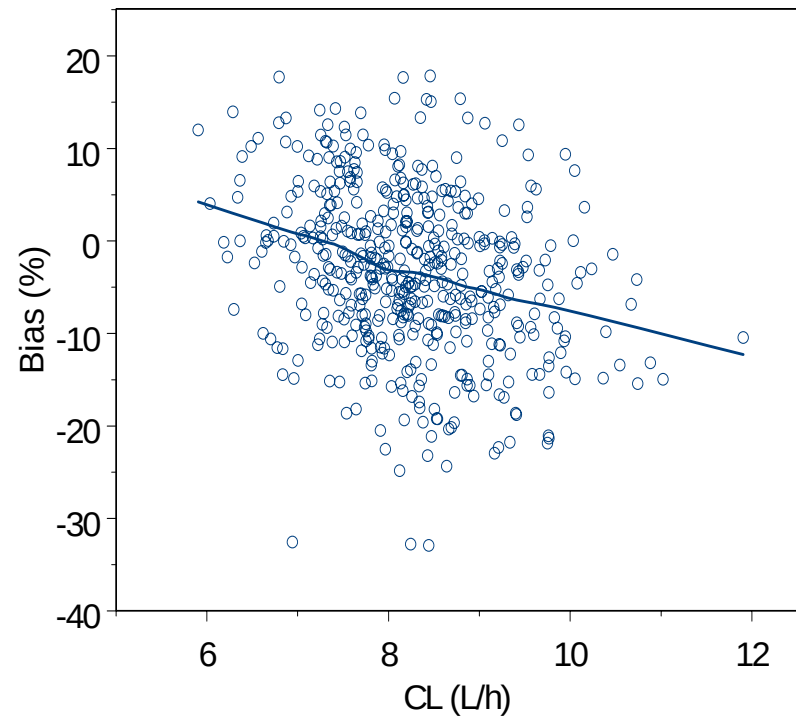
- 24 hour sample added in 50% of patients
- Patients with a sample collected 48 – 96 hours increased to 50%
- Sample fixed at 5 minutes included for both schedules
- Sampling windows adjusted for remaining times

Final Design Results: CL

Drug 1

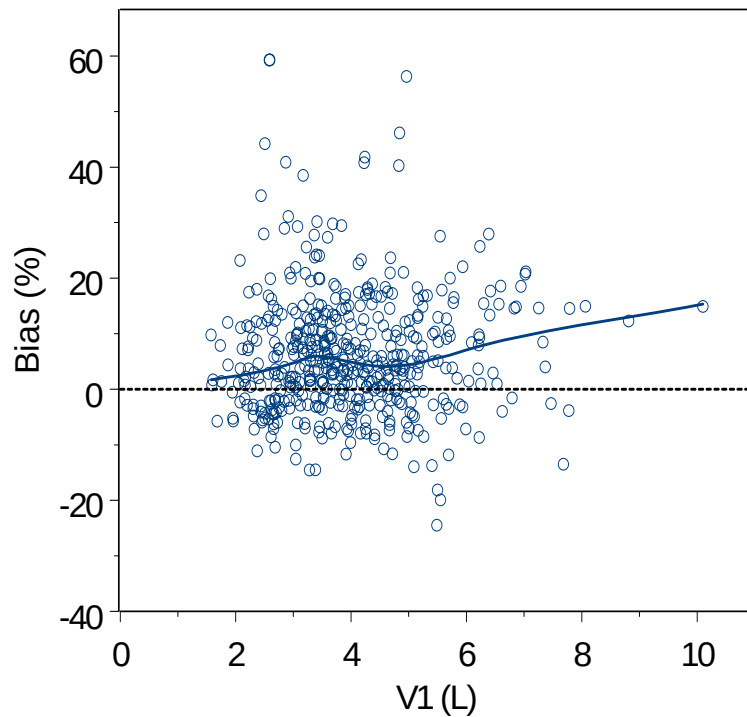


Drug 2

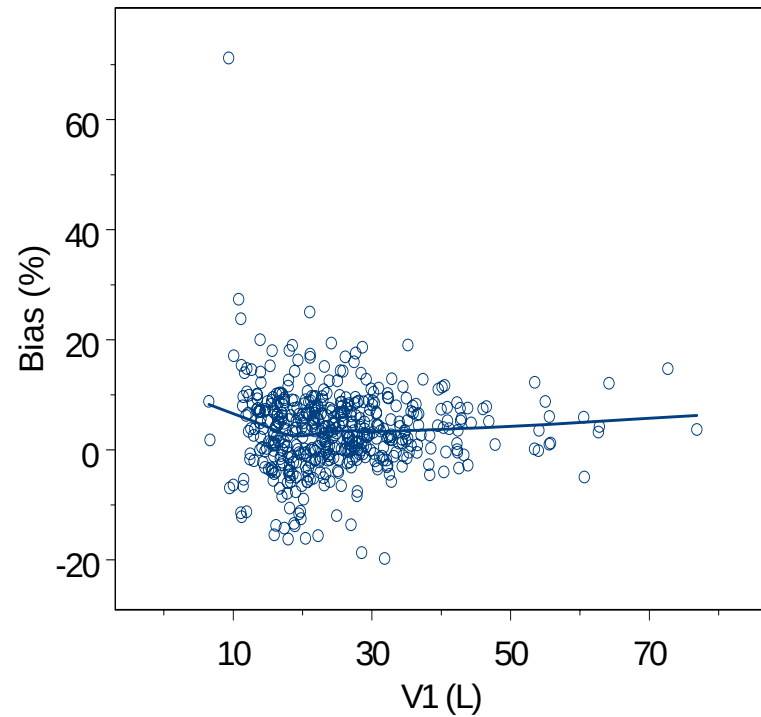


Final Design Results: V

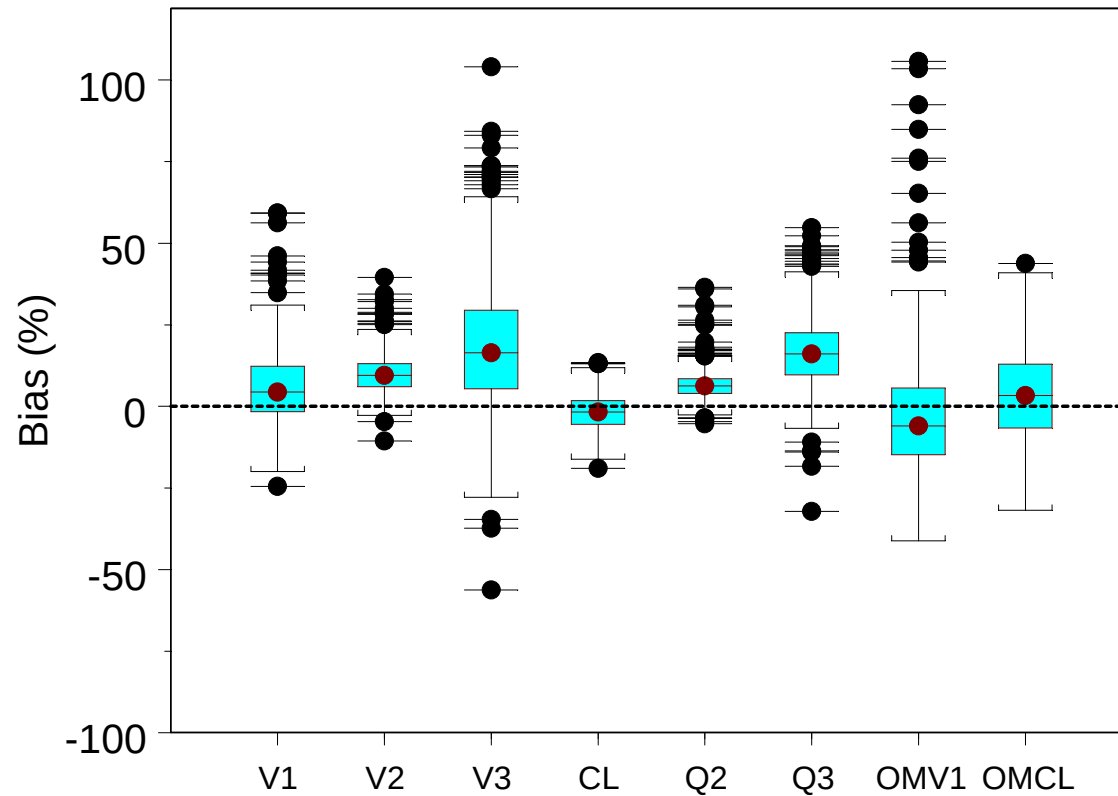
Drug 1



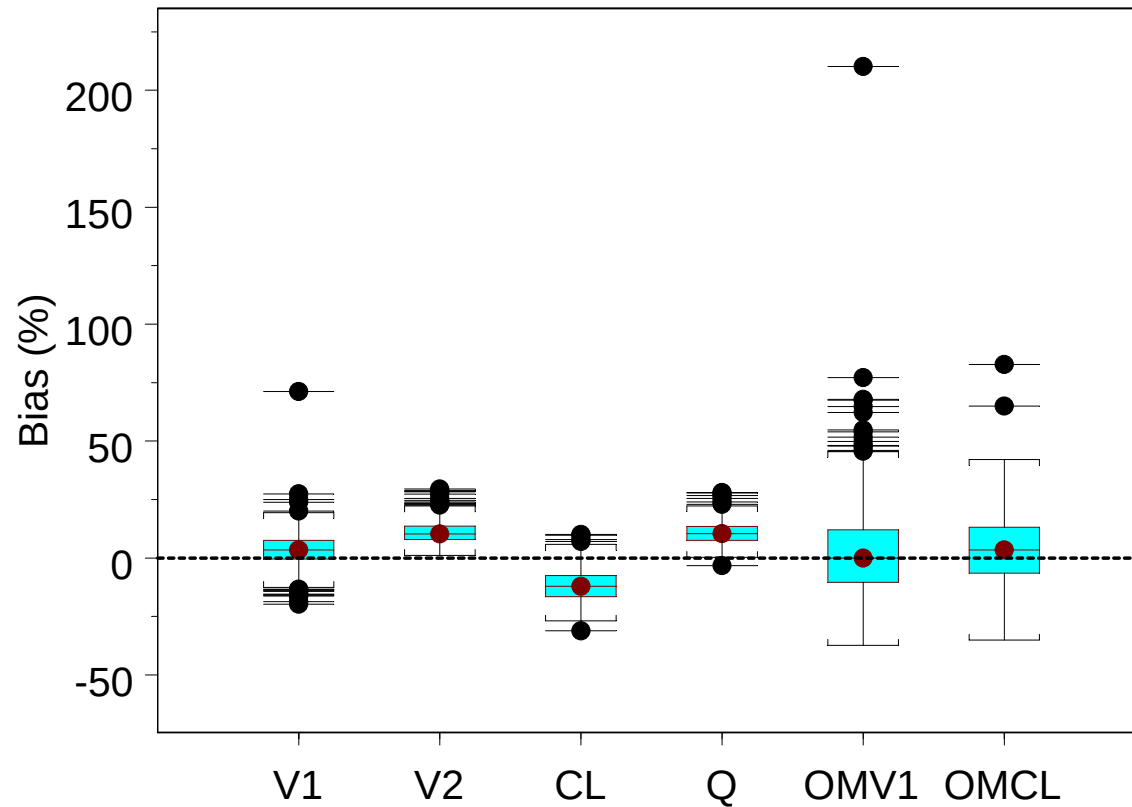
Drug 2



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: Prediction of Trial Outcome Using Simulations with Uncertainty

Example 2: Objectives

- Evaluate the probability of a successful trial under a pre-defined trial design
- Examine sensitivity of this probability estimate to the underlying assumptions
- Endpoint: trough value of the PD marker

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

Specific Aims

Select dose

- To maximize % of patients with trough effect within a specific interval

Estimate

- % of patients with trough effect above and below the specified interval

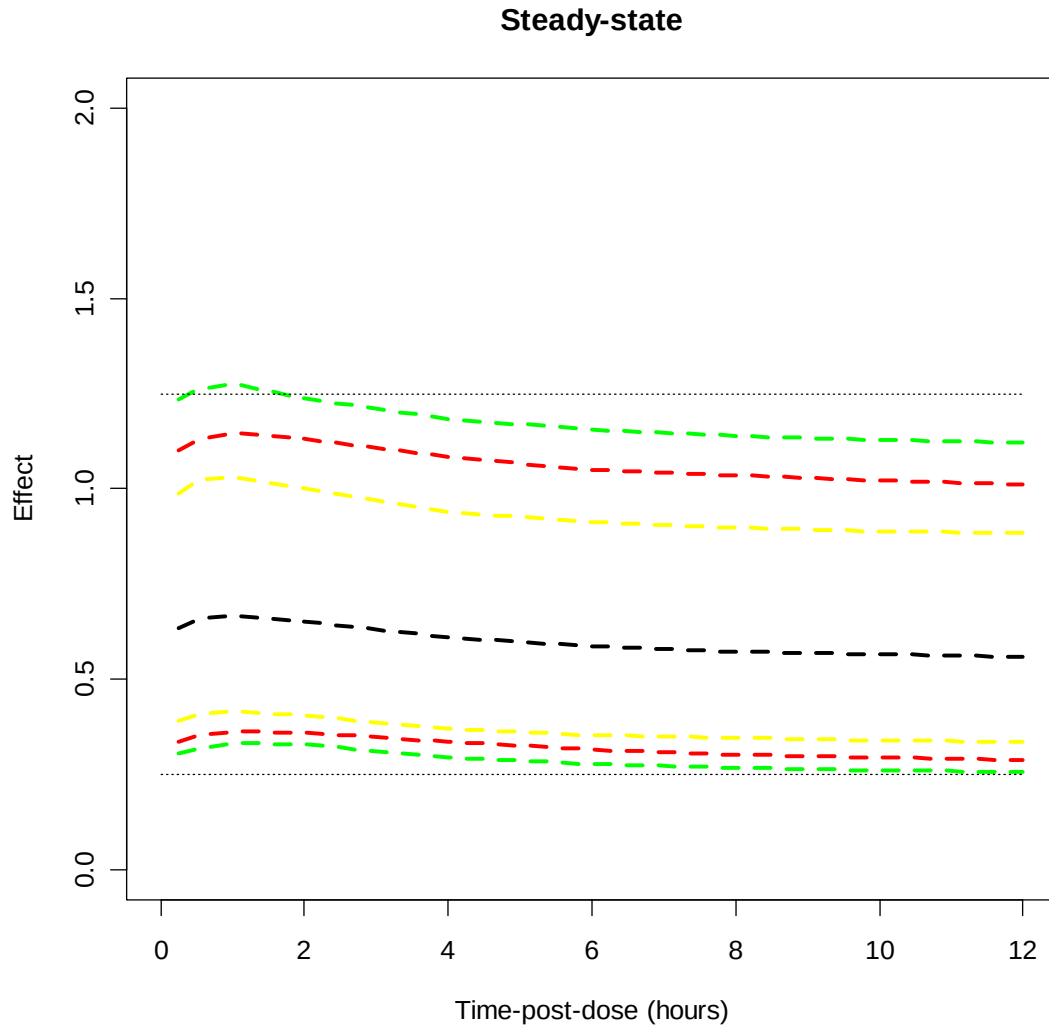
Simulations: Dose Selection Step

- 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 (decrease of uncertainty)

No Uncertainty in Model Parameters



Effect-time course:

Black: median

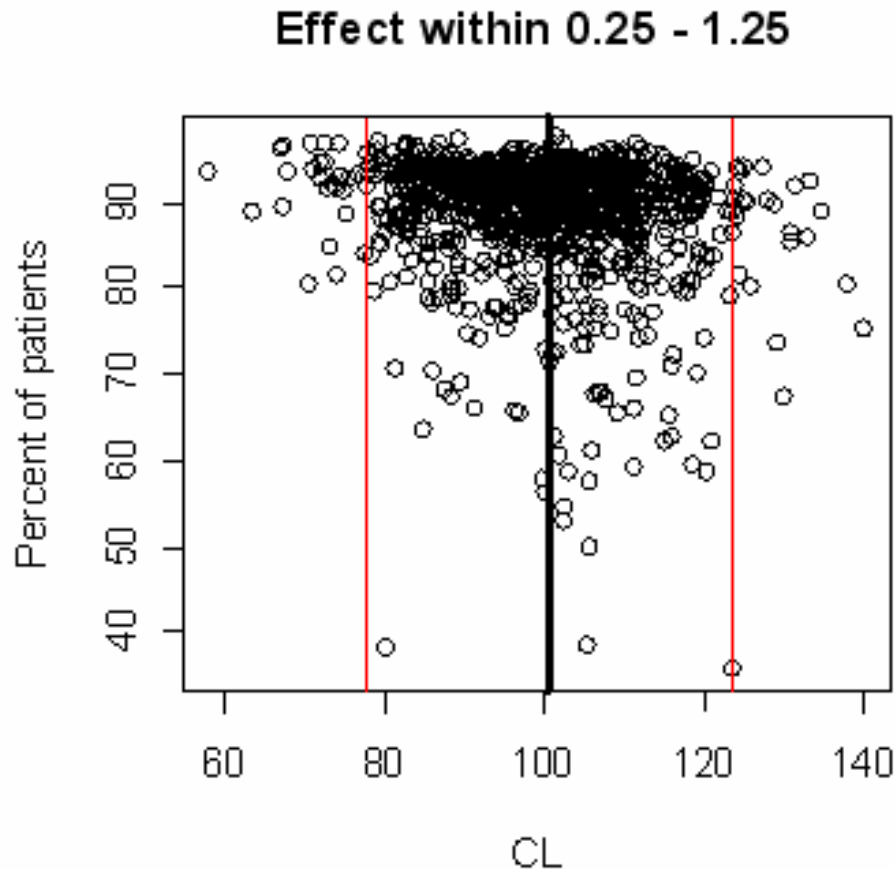
Yellow: 80% CI

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:

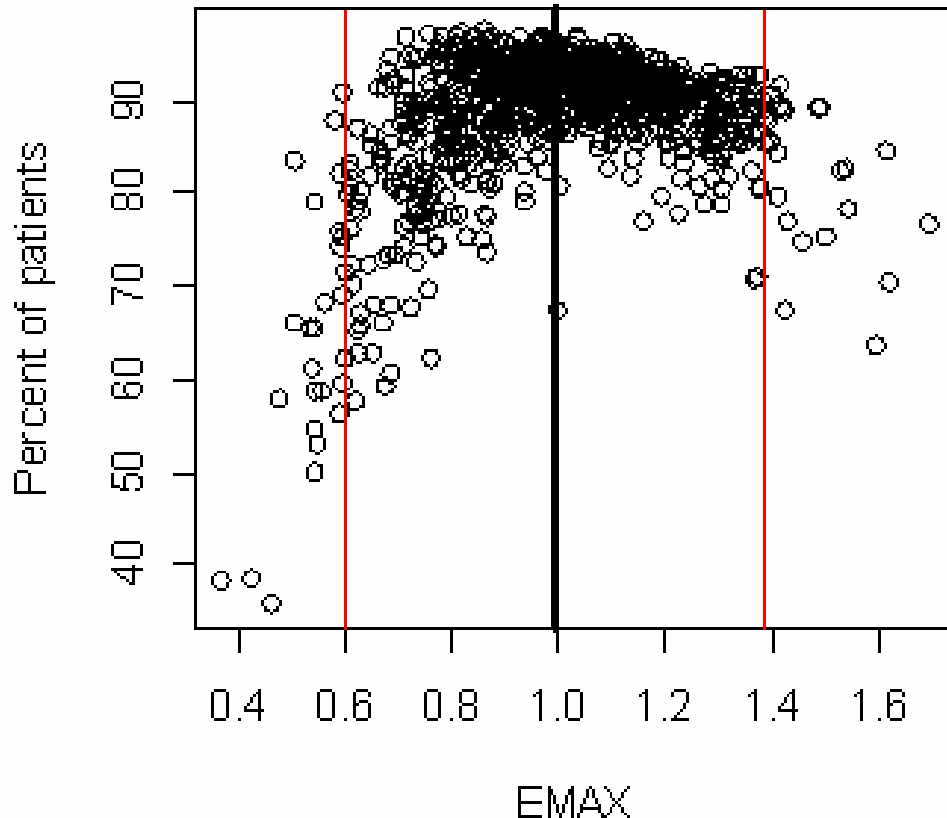
Black: median

Red: 95% CI

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

Uncertainty in PD Parameters

Effect within 0.25 - 1.25



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

Simulated EMAX:

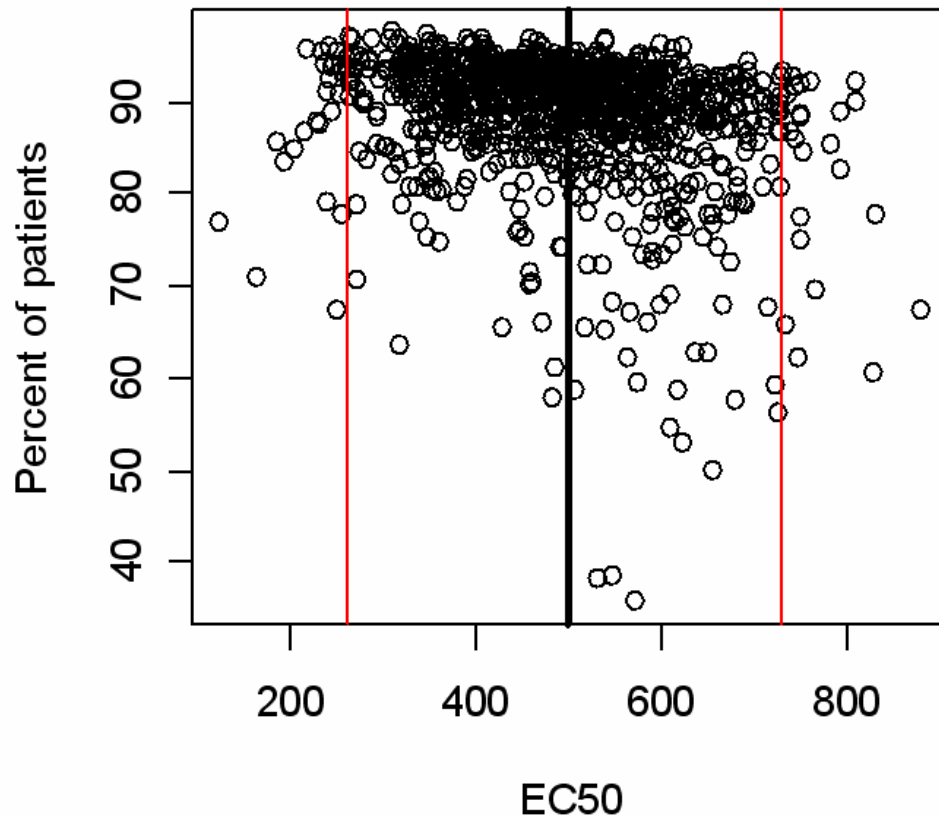
Black: median

Red: 95% CI

Conclusion: Precise knowledge of EMAX is very important

Uncertainty in PD Parameters

Effect within 0.25 - 1.25



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

Simulated EC50:

Black: median

Red: 95% CI

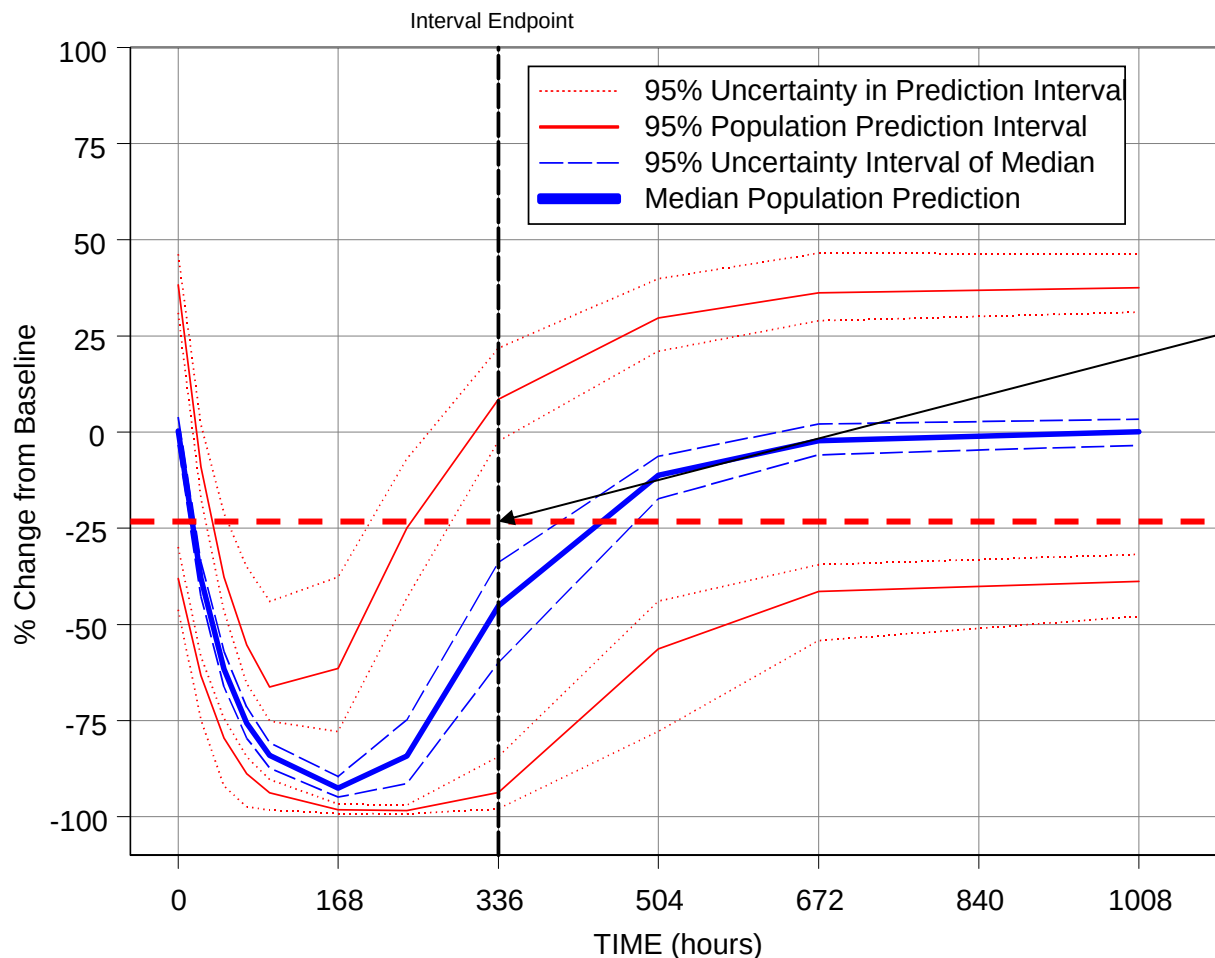
Conclusion: Uncertainty in EC50 is less important than uncertainty in EMAX

Conclusions for Example 2

- 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

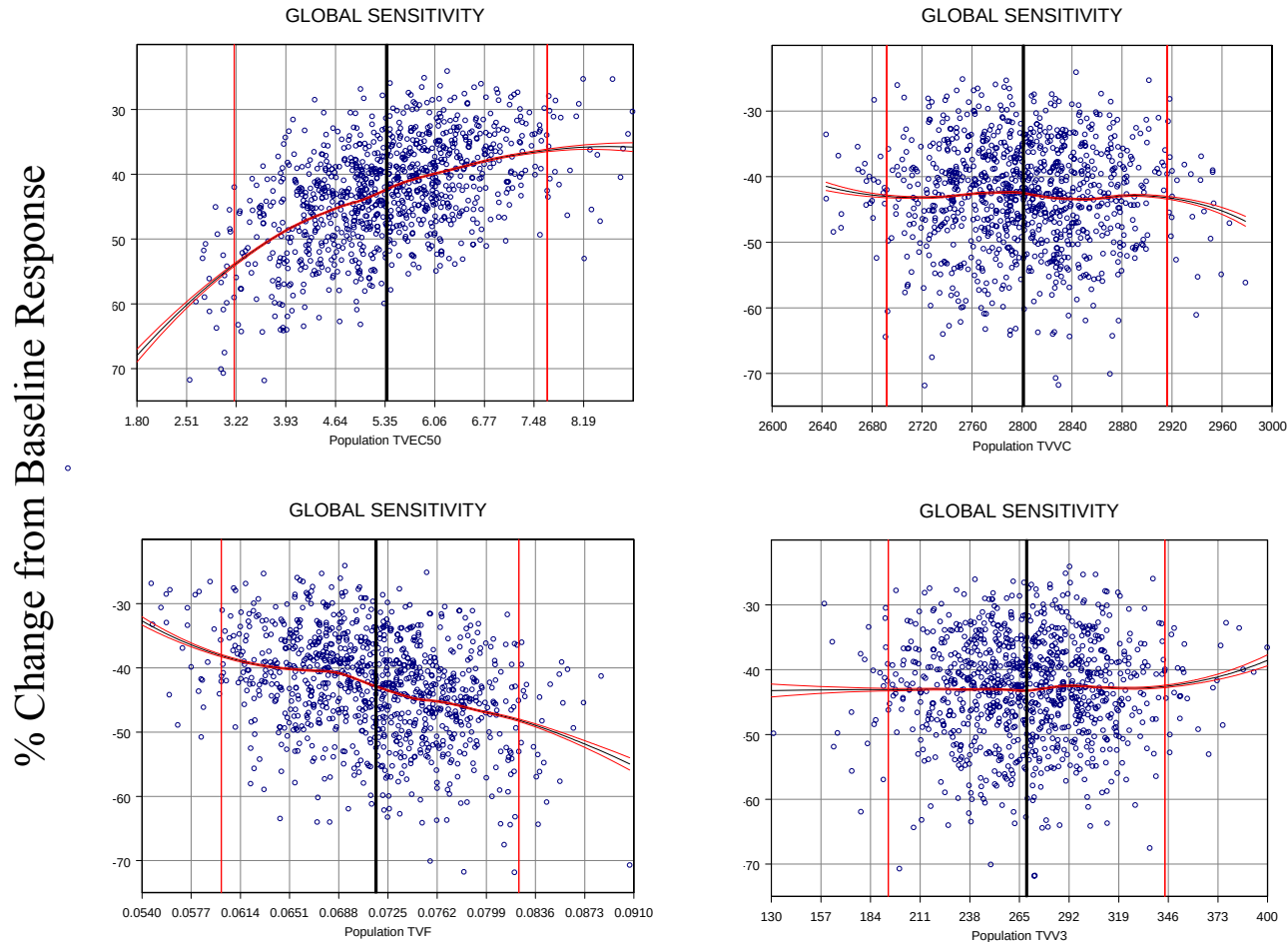
Example 3

View Population Variability and Uncertainty in Prediction (new dose and regimen)



Competing therapy mean response at 2 weeks.

Sensitivity of Simulation Endpoint to Parameter Assumptions



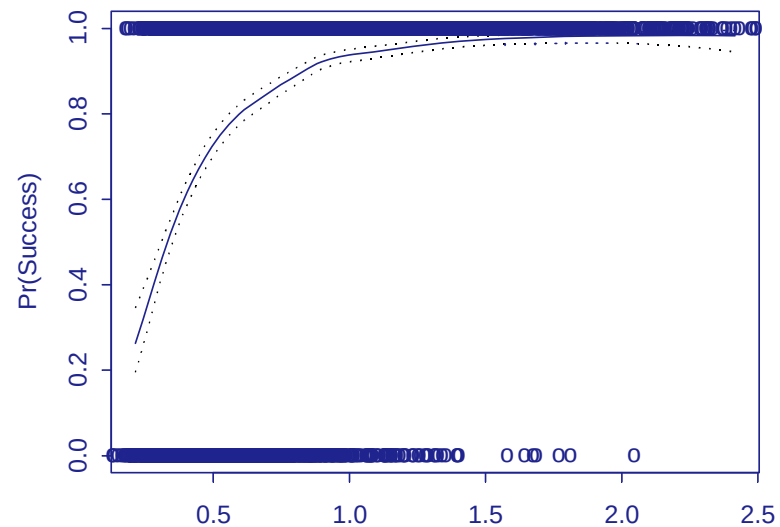
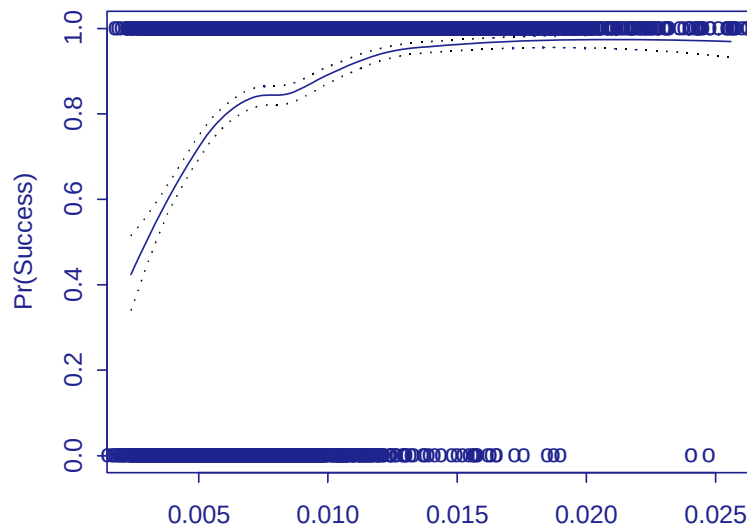
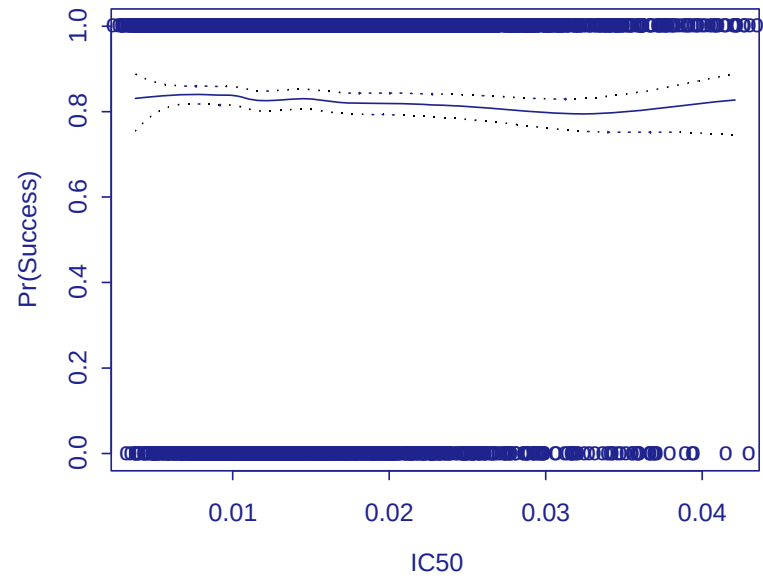
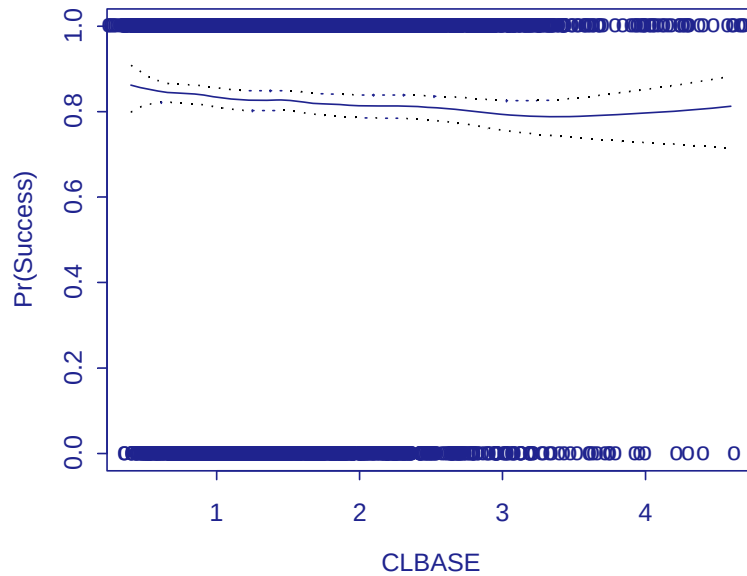
Example 4

Results of Local Sensitivity Analysis

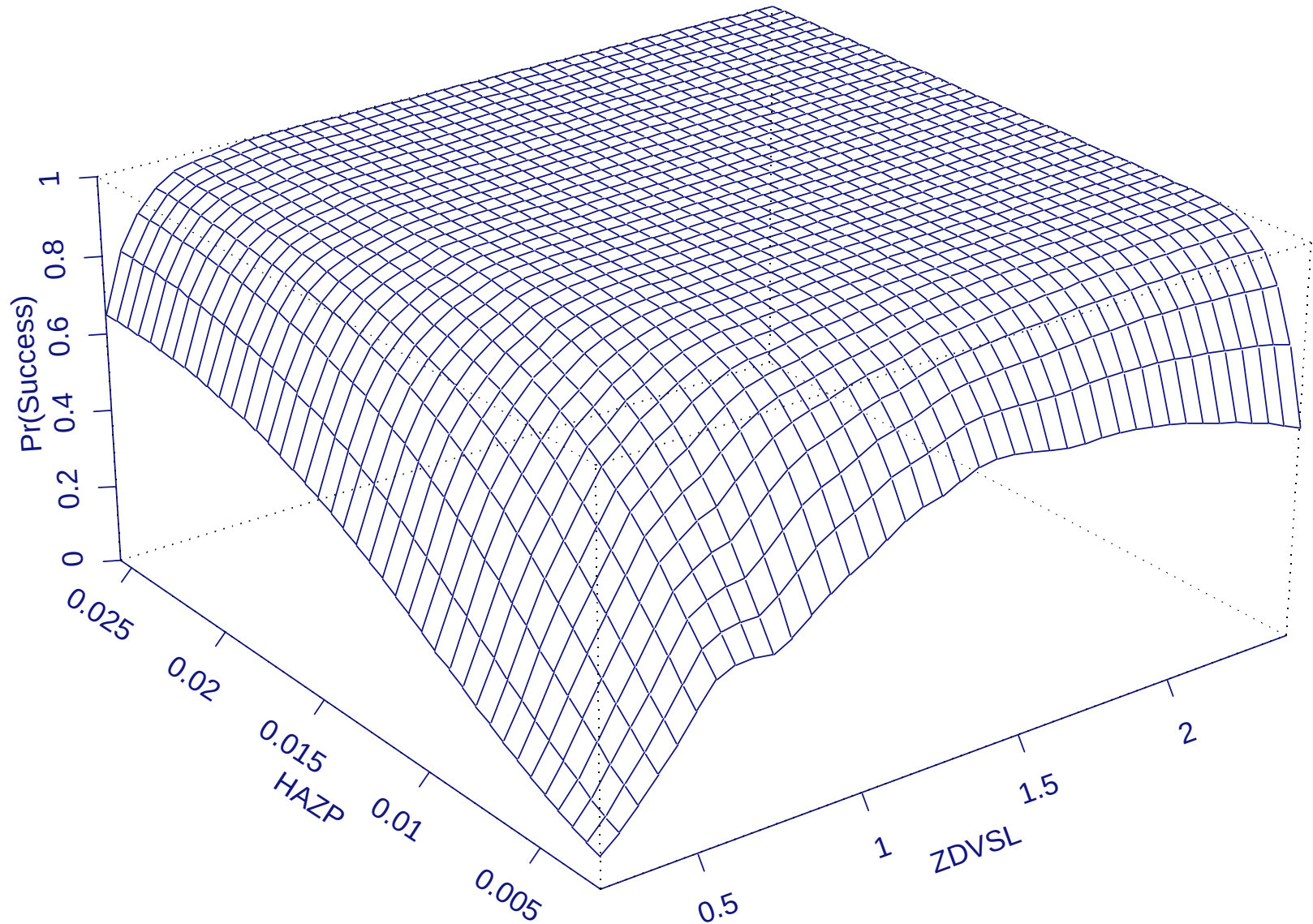
Fixed Value of ZDVSL	% Trials Successful ^a
0.25	30.6%
0.5	70.4%
0.735	93.0%
1.0	99.0%

^aResults reflect 500 simulated trials of 2000 patients

Global Sensitivity Analysis: Probability of Successful Trial

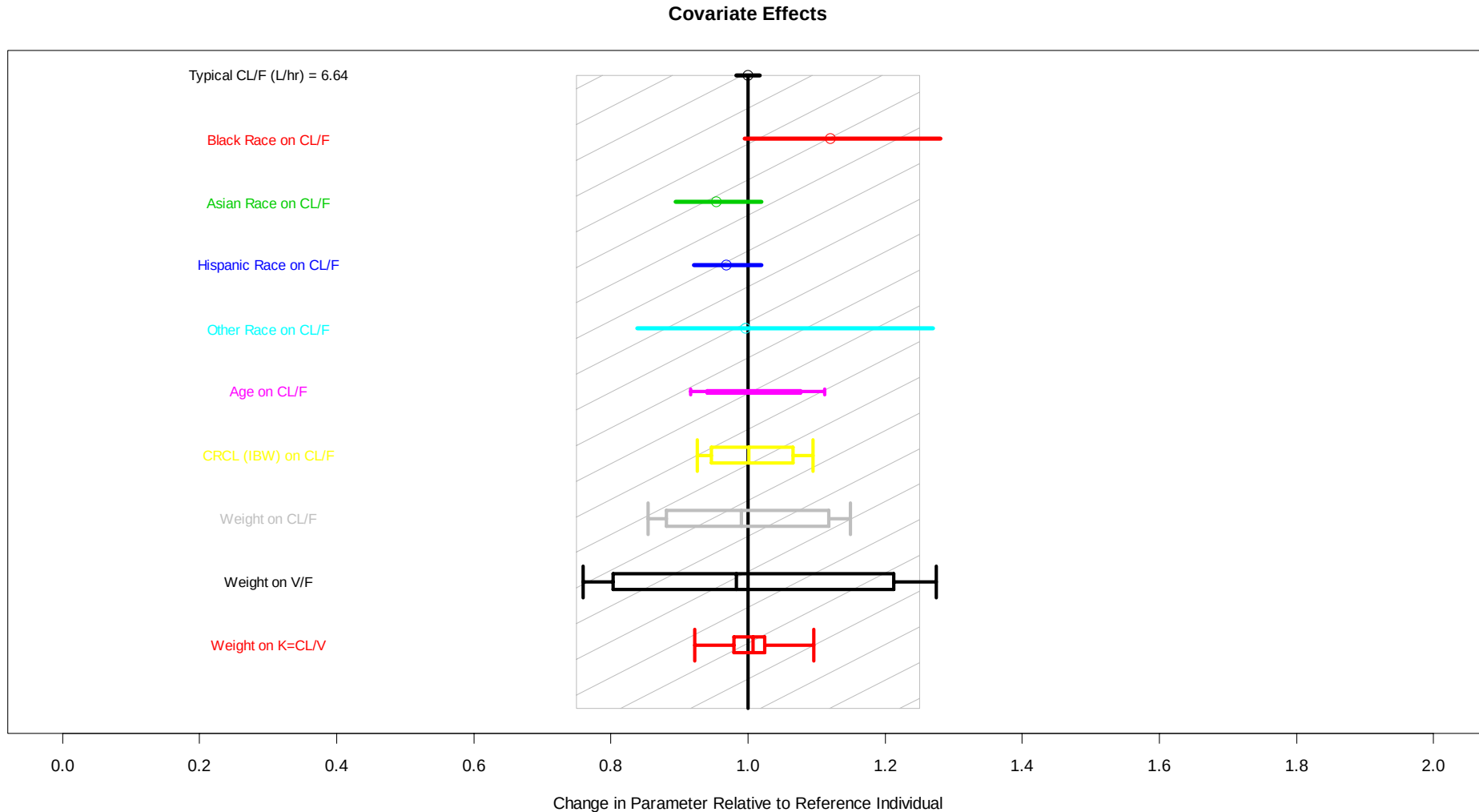


Sensitivity Analysis Surface: Most Influential Parameters



Example 5

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



Summary of Examples

- Predictions of expected responses should be viewed in the context of the uncertainty around the prediction
- Simulation results should include a measure of uncertainty
- Sensitivity analysis in CTS allows for a 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 special tools but it is 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)

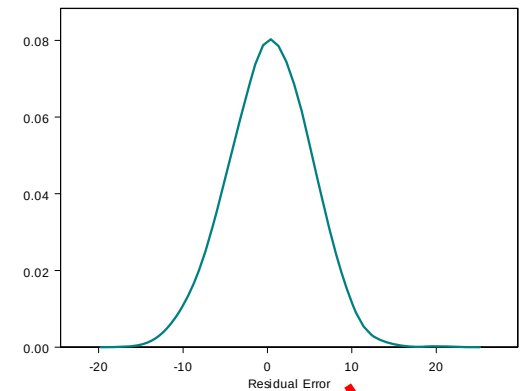
Simulation Plan

- 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 our 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 $(0, \sigma^2)$ per observation, constant fixed-effect parameters (θ)
- Inter-individual error (η) in parameter
 - 1 draw from $(0, \omega^2)$ per individual, constant fixed-effect parameters (θ)
- Uncertainty in models and parameters
 - 1 draw from prior distribution for θ, Ω, Σ per trial

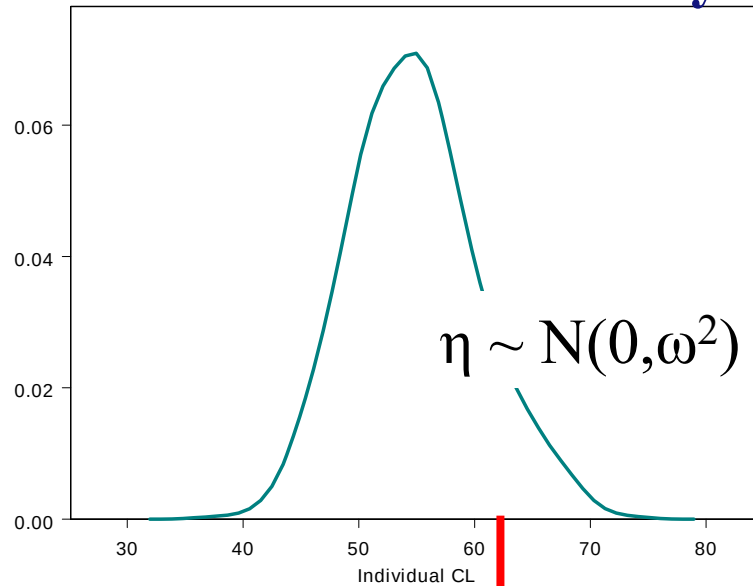
Residual Variability



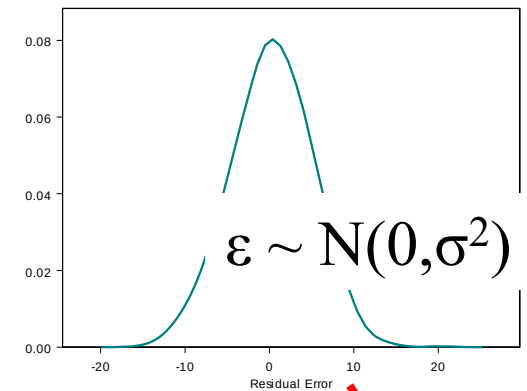
$$C_t = D/V * e^{-CLi/V * t} + \epsilon_t$$

A red arrow points from the ϵ_t term in the equation to the 'Residual Error' label on the x-axis of the graph above.

Interindividual Variability: CL



Residual Variability

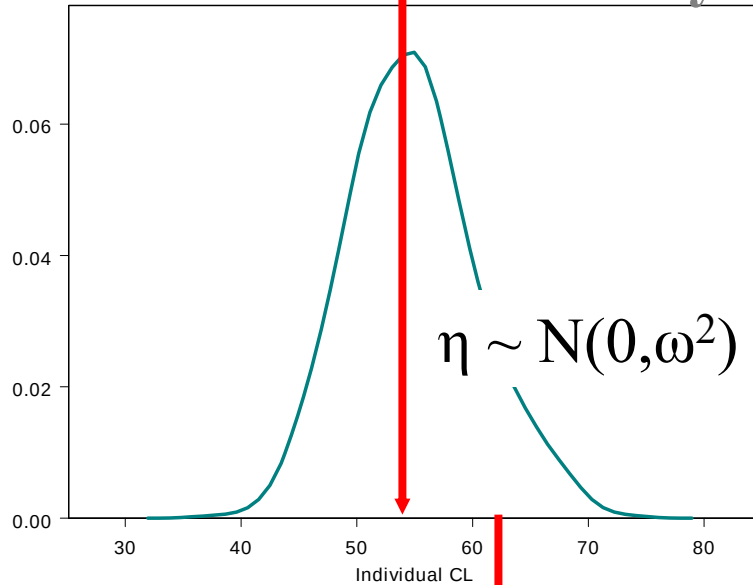


$$C_t = D/V * e^{-CLi/V * t} + \varepsilon_t$$

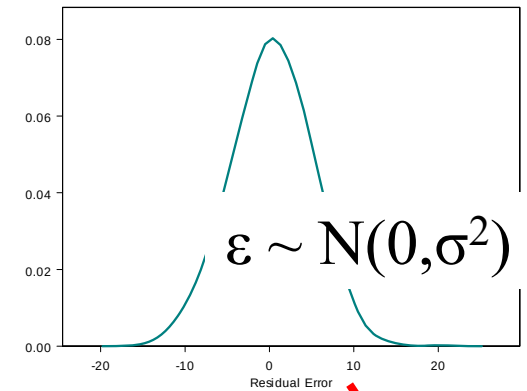
A red arrow points from the ε_t term in the equation to the Residual Error plot above it. Another red arrow points from the CLi term in the equation to the Individual CL plot above it.

TVCL

Interindividual Variability: CL



Residual Variability

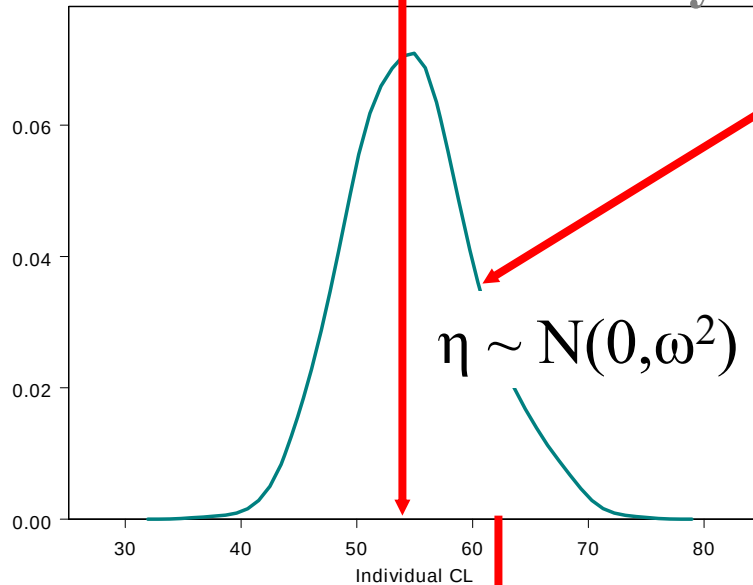


$$C_t = D/V * e^{-CLi/V * t} + \varepsilon_t$$

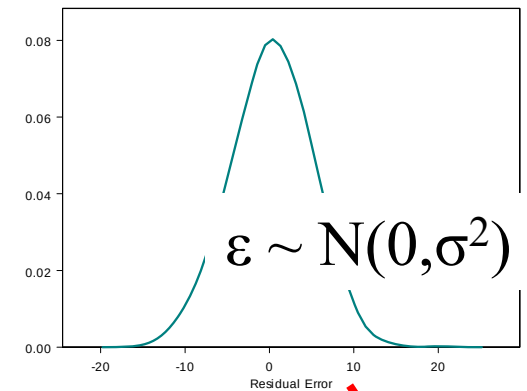
TVCL

Population Variance in CL

Interindividual Variability: CL

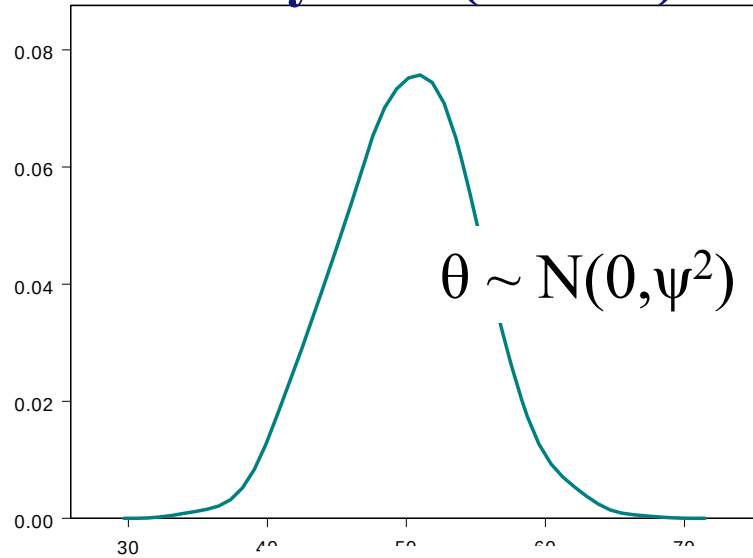


Residual Variability



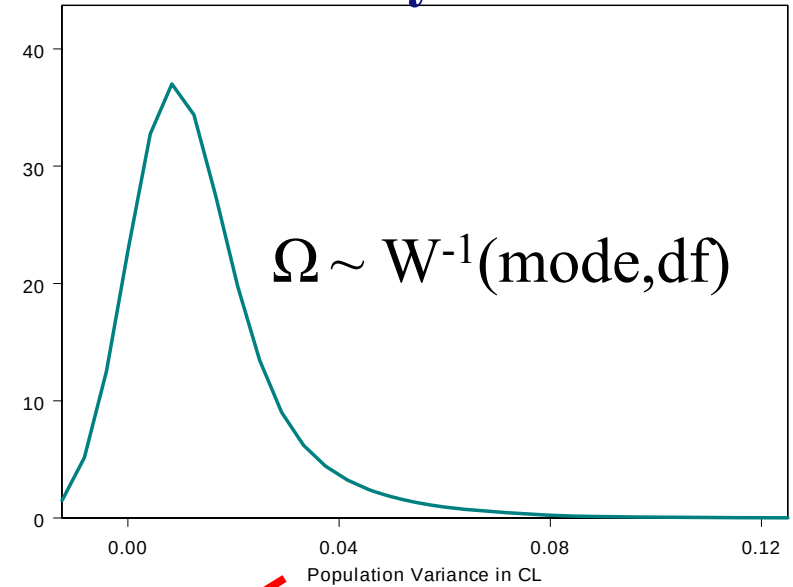
$$C_t = D/V * e^{-CLi/V * t} + \varepsilon_t$$

Uncertainty in $\ln(\text{TVCL})$

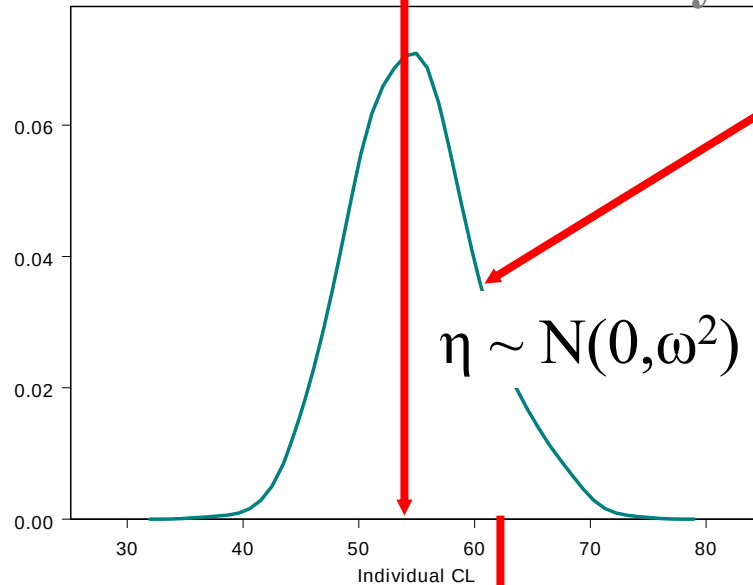


$$\text{TVCL} = \exp(\theta)$$

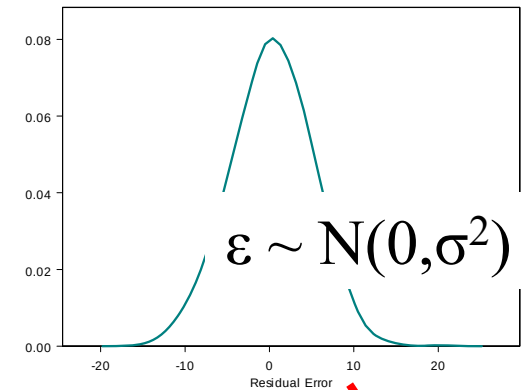
Uncertainty in Var CL



Interindividual Variability: CL



Residual Variability



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

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)

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 populatino 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

Sample from Uncertainty Distributions

R 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=""))

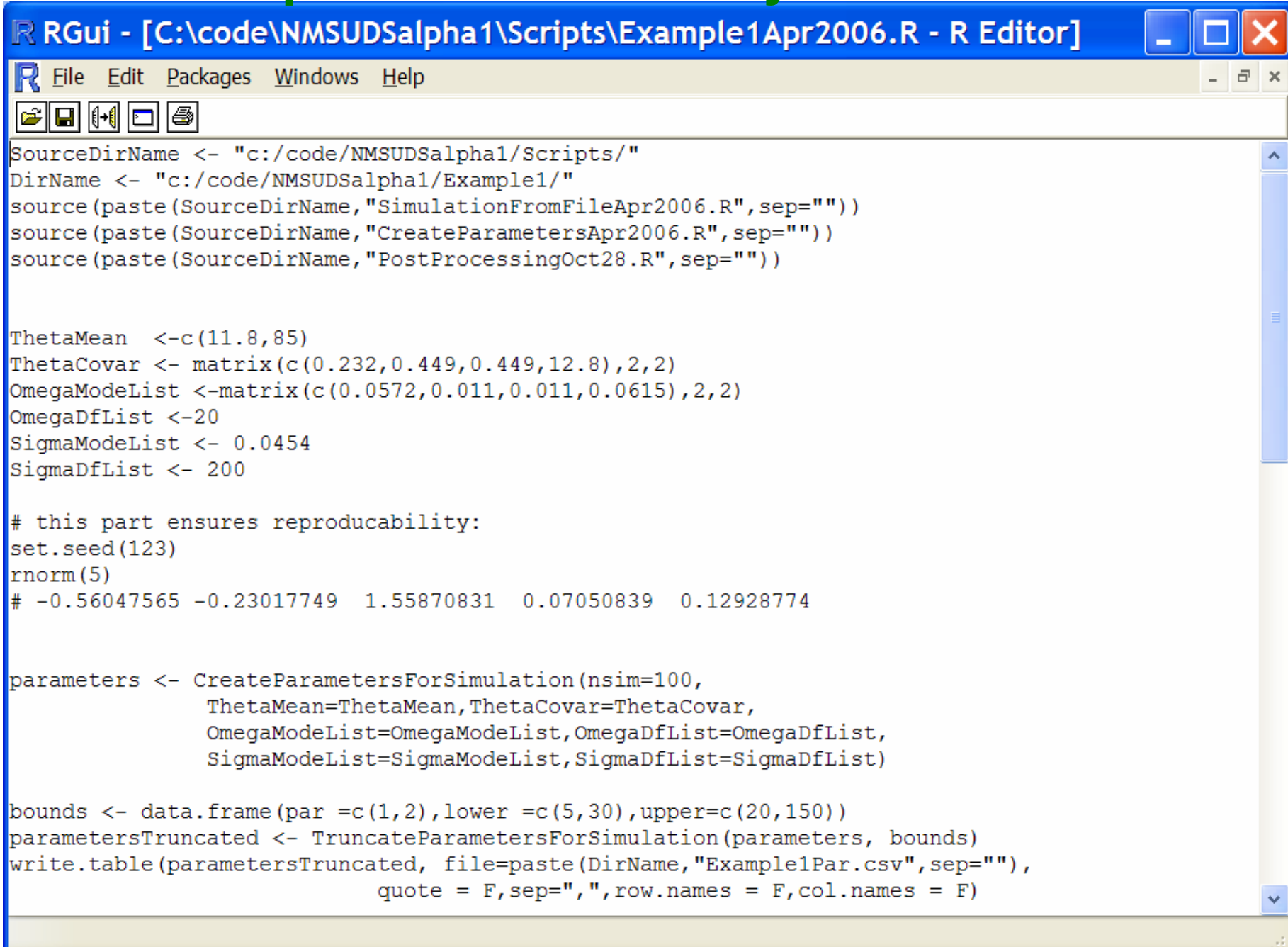
ThetaMean <- c(100, 1000, 7500, 500, 0.5, 1, 500)
ThetaCovar <- diag(c(150, 15000, 1000000, 6400, 0.1, 0.04, 15000))
OmegaModeList <- list(0.04, 0.09, 1, 0.09, 0.25)
OmegaDfList <- c(50, 50, 50, 50, 50)
SigmaModeList <- list(0.04, 0.04)
SigmaDfList <- c(75, 75)

# this part ensures reproducibility:
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



The image shows a screenshot of the RGui application window. The title bar reads "RGui - [C:\code\NMSUDSalpha1\Scripts\Example1Apr2006.R - R Editor]". The menu bar includes "File", "Edit", "Packages", "Windows", and "Help". Below the menu bar is a toolbar with icons for file operations. The main text area contains R code for setting up a simulation, including file paths, parameter matrices, and a truncated parameter generation function. The code is as follows:

```
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 reproducibility:
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.)

Microsoft Excel - Example2Par.csv

Type a question for help

File Edit View Insert Format Tools Data Window Help Adobe PDF

100%

B

A1 97.42

	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						929	0.05571	0.0548
18	102.1	1005	8338	637	0.4987	0.98						999	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
28	98.59	1128	8954	572.9	0.7599	0.8698	222.9	0.03349	0.1218	1.154	0.1108	0.2289	0.04089	0.06008

Example2Par

1 full set of simulation parameters per trial (each row = 1 trial)

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))

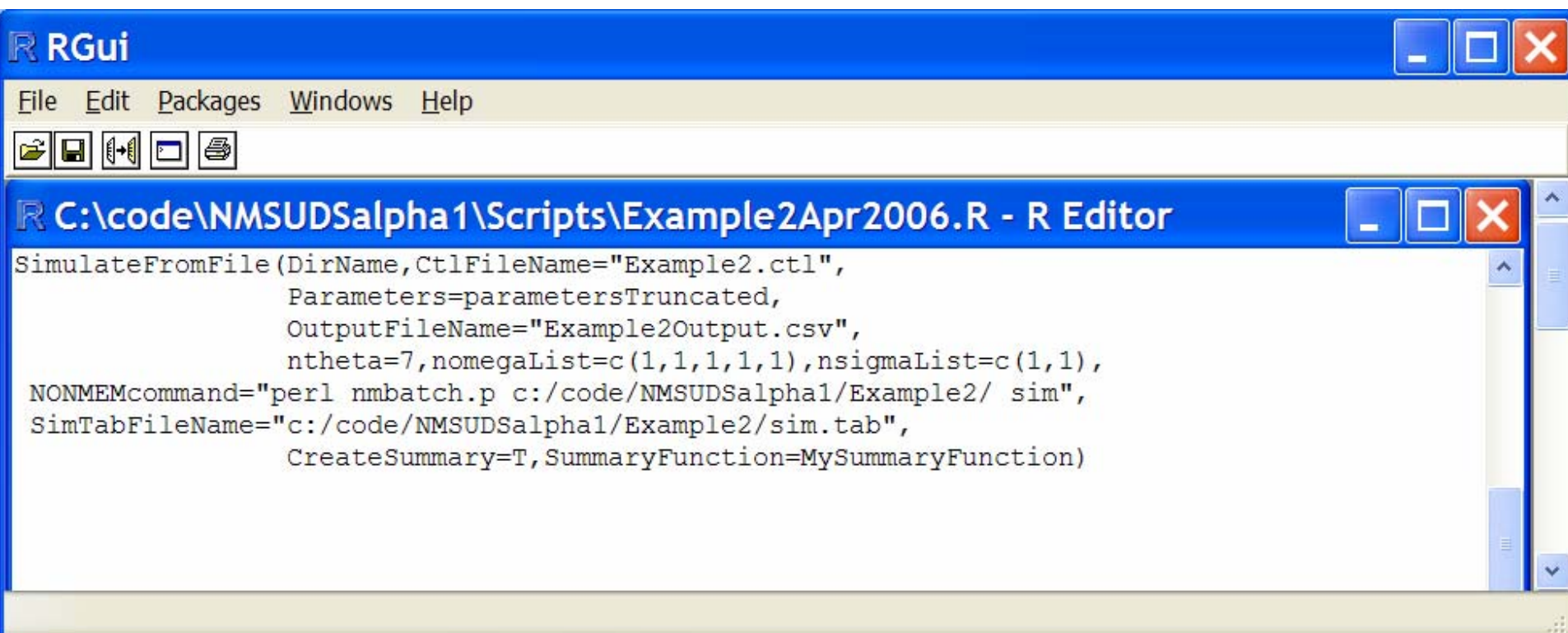
$THETA
100      ; 1 TVCL
1000     ; 2 TVV2
7500     ; 3 TVV3
500      ; 4 TVQ
0.5      ; 5 TVKA
1        ; 6 EMAX
500      ; 7 EC50
$OMEGA
0.04     ; 1 CL
0.09     ; 2 V2
1.00     ; 3 KA
0.09     ; 4 EMAX
0.25     ; 5 EC50
$SIGMA
0.01     ; 1 EFF
0.04     ; 2 PK
$SIMULATION (12345) (6789 UNIFORM)
$TABLE 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



The screenshot shows the RGui application window. The title bar reads "RGui". The menu bar includes "File", "Edit", "Packages", "Windows", and "Help". Below the menu bar is a toolbar with icons for opening, saving, undo, redo, and printing. The main window is titled "C:\code\NMSUDSalpha1\Scripts\Example2Apr2006.R - R Editor". It contains the following R code:

```
SimulateFromFile(DirName, CtlFileName="Example2.ct1",  
                Parameters=parametersTruncated,  
                OutputFileName="Example2Output.csv",  
                ntheta=7, nomegaList=c(1,1,1,1,1), nsigmaList=c(1,1),  
                NONMEMcommand="perl nmbatch.p c:/code/NMSUDSalpha1/Example2/ sim",  
                SimTabFileName="c:/code/NMSUDSalpha1/Example2/sim.tab",  
                CreateSummary=T, SummaryFunction=MySummaryFunction)
```

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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Downloads

The following are available for download from this site.

- [NMQual resources](#): Download source code and documentation for Metrum Institute's free NONMEM® installer.
- [Qpharm Update](#): A periodical of quantitative pharmacology; including reviews and summaries of methods and applied research, discussion groups, recent meetings and upcoming events.
- [G77 utility](#): Download Metrum Institute's redistribution of a popular Fortran77 compiler for Windows. Works great with NMQual!
- [MD5 utility](#): Don't have your own MD5 checksum software? Here's a simple Perl tool that can help you verify other downloads on this page.
- [NMSUDS](#): Download source code and documentation for Metrum Institute's NMSUDS (alpha 1 release) toolbox. This R/ NONMEM® Toolbox for Simulations from Uncertainty DistributionS allows the implementation of parameter uncertainty as an additional level in the random effects hierarchy and can be used with simulation models defined in NONMEM® and/or R. As the version indicates, this is work in progress; feel free to experiment, and use at your own risk. Please provide feedback to NMSUDS@metruminstitute.org. NMSUDS is distributed under GPL.

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Acknowledgements

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

Questions or Comments?