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

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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 Endpoint (e.g. mean response)

2.5% = 4.16
97.5% = 5.42

2.5% = 4.61
97.5% = 5.85

simulation without uncertainty (red)
Simulation with Uncertainty Results

Reference response

Probability that mean response > reference:
No uncertainty: 100%; With uncertainty: 94%

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 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

• 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

<table>
<thead>
<tr>
<th>Fixed Value of ZDVSL</th>
<th>% Trials Successful&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25</td>
<td>30.6%</td>
</tr>
<tr>
<td>0.5</td>
<td>70.4%</td>
</tr>
<tr>
<td>0.735</td>
<td>93.0%</td>
</tr>
<tr>
<td>1.0</td>
<td>99.0%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Results reflect 500 simulated trials of 2000 patients
Global Sensitivity Analysis: Probability of Successful Trial

Simulations with Uncertainty

HAZP Copyright 2006, metrum research group llc ZDVSL
Sensitivity Analysis Surface: Most Influential Parameters
Covariate Model for Population PK: Inferences in the Face of Uncertainty

Typical CL/F (L/hr) = 6.64

- Black Race on CL/F
- Asian Race on CL/F
- Hispanic Race on CL/F
- Other Race on CL/F
- Age on CL/F
- CRCL (IBW) on CL/F
- Weight on CL/F
- Weight on V/F
- Weight on K=CL/V

Change in Parameter Relative to Reference Individual
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 ($\varepsilon$)
  - 1 draw from $(0, \sigma^2)$ per observation, constant fixed-effect parameters ($\theta$)

- Inter-individual error ($\eta$) in parameter
  - 1 draw from $(0, \omega^2)$ per individual, constant fixed-effect parameters ($\theta$)

- Uncertainty in models and parameters
  - 1 draw from prior distribution for $\theta$, $\Omega$, $\Sigma$ per trial
Residual Variability

\[ C_t = \frac{D}{V} e^{-CL_i/V \cdot t} + \varepsilon_t \]
Interindividual Variability: CL

\[ \eta \sim N(0, \omega^2) \]

Residual Variability

\[ \varepsilon \sim N(0, \sigma^2) \]

\[ C_t = \frac{D}{V} e^{-CL_i/V \cdot t} + \varepsilon_t \]
Simulations with Uncertainty Copyright 2006, metrum research group LLC

$\text{C}_t = \frac{D}{V} e^{-\text{CL}_i/V*t} + \varepsilon_t$

Interindividual Variability: CL

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

Residual Variability

$\varepsilon \sim N(0, \sigma^2)$
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30 40 50 60 70 80

Individual CL

0.00 0.02 0.04 0.06

Residual Error

0.00 0.02 0.04 0.06 0.08

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

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

\epsilon \sim N(0, \sigma^2)

Population Variance in CL

Residual Variability

Interindividual Variability: CL

TVCL

\eta \sim N(0, \omega^2)
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Uncertainty in ln(TVCL)

\[ \theta \sim N(0, \psi^2) \]

TVCL = \( \exp(\theta) \)

Interindividual Variability: CL

\[ \eta \sim N(0, \omega^2) \]

Uncertainty in Var CL

\[ \Omega \sim W^{-1}(\text{mode}, \text{df}) \]

Residual Variability

\[ \varepsilon \sim N(0, \sigma^2) \]

\[ C_t = \frac{D}{V} \exp(-CL \frac{t}{V}) + \varepsilon_t \]
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 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 PRI OR 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
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)
OmegaDiFList <- c(50,50,50,50)
SigmaModeList <- list(0.04,0.04)
SigmaDiFList <- 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,
                                          OmegaDiFList=OmegaDiFList,
                                          SigmaModeList=SigmaModeList,
                                          SigmaDiFList=SigmaDiFList)

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

```r
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 0.0705839 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 example](example2par.csv)

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.:
  \[ \text{LNCL} = \text{THETA} \]
  \[ \text{CL} = \text{EXP}(\text{LNCL}) \]
- 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
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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Questions or Comments?