**Supplemental Material**

Population pharmacokinetic method to predict within-subject variability using single-period clinical data

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**Figure S1.** The predictive success rate for scenarios of the first experiment.



**Figure S2.** The predictive success rate for scenarios of the second experiment.

Table S1. Tabulated summary for results of comparison with and without covariance between omegas

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Evaluation scenario** | | | **Predictive success rate of RV(%)** | |
| **WV(%)** | **IIV(%)** | **No. of subject** | **With Covariance**  **between ω1 and ω2\*** | **Without Covariance between ω1 and ω2\*\*** |
| 50 | 10 | 18 | 52 | 62 |
| 50 | 50 | 18 | 50 | 62 |
| 10 | 50 | 18 | 89 | 88 |

\* Preform of NONMEM PK model for 100 simulation dataset generated by mrgsolve R package, \*\*Perform of NONMEM PK model for 1000 simulation dataset generated by basic R code. The ω1 and ω2 meant IIV on CL and Vd, respectively.

Text S1. Example as a R code for generating simulation dataset

## Individual PK parameters(IIV 10%)

data.sample <- 1:1000

start.number <- min(data.sample)

i <- start.number

for (i in data.sample) {

set.seed(seed[i])

x <- rlnorm(100000, meanlog = 10, sdlog = 1)

y <- rlnorm(100000, meanlog = 50, sdlog = 5)

CL <- sample(log(x)[log(x)>0],12) # Preventing for generating negative number at CL

Vd <- sample(log(y)[log(y)>0],12) # Preventing for generating negative number at Vd

id <-seq(1:12)

data <- data.frame(id,CL,Vd)

write.table(data,paste("data",i,".csv",sep=""),sep=",",row.names = F)

}

## Calulation the concentration using parameters(CL, Vd)

total <- 1:1000

min.total <- min(total)

k <- min.total

for(k in total){

one <- read.table(paste("data",k,".csv",sep=""),sep = ",",header=TRUE)

kel <- one$CL/one$Vd

one <- cbind(one,kel)

number <- 1:12

begin <- min(number)

i <- begin

for(i in number){

special.ID <-DO[DO$ID==i,]

timenumber <- 1:12

time.start <- min(timenumber)

j <- time.start

for(j in timenumber){

#iv PK equation(WV = 0.3)

conco <- (100\*exp(-one$kel[i]\*special.ID$TIME[j])/(one$Vd[i]))

eps <- rnorm(12, mean = 0, sd = 0.3)

eps.sample <- sample(eps,1)

conco2 <- conco\*(1+eps.sample) ##Proportional model

# Preventing for generating negative number at plasma concentration

while(conco2<0){

eps <- rnorm(12, mean = 0, sd = 0.3)

eps.sample <- sample(eps,1)

conco2 <- conco\*(1+eps.sample) ##Proportional model

}

if(j==time.start)

DV <- conco2

else DV <-rbind(DV,conco2)

}

real <- cbind(special.ID, DV)

if(i==begin)

set <- real

else set <-rbind(set, real)

}

write.table(set, paste("CONC",k,".csv",sep = ""),sep = ",", row.names = FALSE)}

Text S2. C++ and R script code when used mrgsolve R package

## Example of CPP file

$PROB

- 1 COMP iv PK model

- Random effect : yes

$PARAM

TVCL = 10

TVV = 50

$CMT

CENT

$MAIN

double CL=TVCL\*exp(ETA(1));

double V=TVV\*exp(ETA(2));

$ODE

dxdt\_CENT = -(CL/V)\*CENT;

$OMEGA >> annotated=TRUE, block = TRUE

ECL: ETA on Clearance

EV: ETA on Volume

0.25

0.0625 0.25

$SIGMA

0.25

$TABLE

double IPRED = CENT/V;

double DV = IPRED\*(1+EPS(1));

$CAPTURE

DV IPRED

## Example of R script file

# problem : WV0.5\_IIV0.5\_omegacovariance0.5

# subject NO. = 18

# load packages

library(mrgsolve)

library(tidyverse)

library(dplyr)

# giving seed number

set.seed(20191203)

# loading cpp file

mod<-mread("WV0.5\_IIV0.5\_COV0.5","C:/Users/Wonho Kang/Desktop/TEST\_OMBLOCK/WV0.5\_IIV0.5\_COV0.5/N18")

total <- 1:100

min.total <- min(total)

i <- min.total

for(i in total){

nn=18

idata<-tibble(ID=seq(nn))

tmptolerance = -1

tmpcount = 0

while (tmptolerance < 0){

tmpcount = tmpcount +1

df<-mod %>%

ev(amt=100) %>%

idata\_set(idata) %>%

mrgsim(end=24, delta=0.1) %>%

filter(time==0|time==0.083|time==0.167|time==0.333|time==0.5|time==1|time==2|time==4|time==6|time==8|time==12|time==24 )

tmptolerance = min(df$DV)

print(tmpcount)

}

#add MDV

df<-df %>% mutate(MDV=0)

df$MDV[which(df$DV==0)]<-1

#add AMT

df<-df %>% mutate(AMT=0)

df$AMT[which(df$MDV==1)]<-100

#rename TIME

df<-df %>% rename(TIME=time)

df<-df %>% arrange(ID,TIME)

df<-df[c("ID","TIME","DV","MDV","AMT")]

names(df) <- c("#ID","TIME","DV","MDV","AMT")

write.table(df,paste("datafile",i,".csv",sep = ""),sep = ",",quote=FALSE,row.names=FALSE)

}

Text S3. NONMEM PK Model code

$PROBLEM Simulation dataset2\_IIV50%\_WV30%\_N18

$INPUT ID TIME DV MDV AMT

$DATA datafile1.csv IGNORE=@

$SUBROUTINES ADVAN6 TOL=8

$MODEL

COMP (CENT, DEFDOSE, DEFOBS)

$PK

CL = THETA(1) \* EXP(ETA(1))

V = THETA(2) \* EXP(ETA(2))

KEL = CL/V

S1=V

$DES

DADT(1) = -KEL\*A(1)

$ERROR

IPRED = F

DEL=0

IF(IPRED.EQ.0) DEL=1

W=IPRED+DEL

IRES = DV-IPRED

IWRES = IRES/W

Y = F+W\*EPS(1)

$THETA

(0, 10) ; CL

(0, 50) ; V

$OMEGA

0.25

0.25

$SIGMA

0.09

$EST METHOD=1 MAXEVAL=9999 NOABORT INTER PRINT=5 NSIG=2 SIGL=8

$TABLE ID TIME DV MDV AMT IPRED IWRES CWRES ONEHEADER NOPRINT FILE = sdtab1

$TABLE ID ETA1 ETA2 ONEHEADER NOPRINT FILE = patab1