PKPD Modeling of Continuous and Categorical data in NONMEM 7

Hands-On Session – Disease progression modeling

Modeling effect of moxonidine on noradrenaline (NA) concentrations

Introduction:

This exercise makes use of the NA data from the moxonidine trial. It aims at demonstrating some aspects of baseline, direct drug effect and disease progression modelling as well as some PsN and Xpose functionality. The first-order (FO) method is used during model building for the sake of run-time. Log-transformed data (DV) are used.

Files provided:

Data set:

data1.csv		NA data from moxonidine trial

Model files:

run1.mod	=	baseline model using placebo data only. Start model building from this model
run5.mod	=	model with a linear disease progression model. Start model for evaluating drug effects based on treatment data.

Other files:

psn_vpc_command.txt	=	command for running vpc in PsN
xpose_vpc_commands_run1.R	=	R-script to plot vpc-results within Xpose

Tasks:

1) Analyse placebo data only

   a. Run the model using placebo data only.
   Note that $DATA "IGN (DOSE.GT.0)" omits treatment data.
   To run the model with PsN type "execute run1.mod" at the prompt.
   "sumo run1.lst" gives you a summary of the results. What files have NONMEM 7 created?

   b. Perform and assess the VPC from run1.mod (see Fig. 1 on next page). Use the PsN and Xpose commands in the files provided.

   c. Evaluate a linear disease progression model (without IIV) in NONMEM.
   DS = BASE*(1+ALPHA*TIME/24/7)
   You can use the following PsN command to create a new model file:
   `update_inits run1.mod –out=run2.mod`

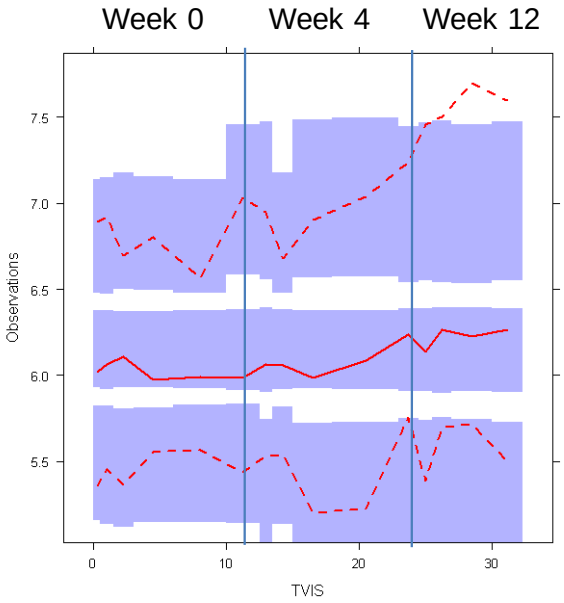

Fig 1. VPC of run 1 (95% PI). The solid line represents the median of the observed data and the dashed lines the 2.5th and 97.5th percentiles of the observed data. Blue shaded areas are the confidence intervals based on the simulated data's 2.5^{th,} 50th and 97.5th percentile. TVIS=0-12 is week 0, TVIS=12-24 is week 4 and TVIS=24-36 is week 12.
The Xpose command for running this model is provided in an R-script in the Files provided folder:

```
xpose.VPC(vpc.info="vpc1/vpc_results.csv",vpctab="vpc1/vpctab1",
PI="NULL", PI.ci="area", PI.real=TRUE, type="n")
```

2) <u>Analyse treatment data only</u>
   a. Run the best model from 1) using treatment data only (e.g. run5.mod provided in the Files_provided folder). The IGNORE statement in $DATA is changed to "IGN (DOSE.LE.0)". All model parameters based on placebo data are fixed to the estimates obtained in step 1.

   b. Investigate a direct Emax model for the (inhibitory) influence of drug concentration on NA concentrations. Assume IIV in EC_{50} only.

   c. Investigate an offset drug effect on disease progression. Parameterize as follows;
   OFFSET=0
   IF(DOSE.GT.0.AND.VISI.GT.3) OFFSET= THETA(.)
   DS = BASE*(1+ALPHA*(TIME/24/7-OFFSET)) * (1-EFF)
   What assumptions does this parameterization make?

   d. * Investigate a similar protective drug effect model on disease progression.

3) <u>***** Analyse all data</u>

a. From the best model in step 2 estimate all parameters using all data (omit IGNORE statement). Are there any pronounced changes in the parameters describing baseline and disease progression?

b. Investigate correlation between baseline variability and drug effect variability.

c. Make a VPC for the preferred model (runx.mod) using stratification (STRT=1 is moxonidine treated and STRT=2 is placebo treated).

PsN command : `vpc runx.mod -lst=runx.lst -samples=200 -dir=vpcx -bin_by_count=0 -idv=TVIS -bin_array=.5,1.5,3,6,10,12.5,13.5,15,18,23,24.5,25.5,27,30 -stratify_on=STRT -seed=123`

(The simulations may take some time, the files needed to produce vpc in Xpose are provided in Solutions folder, directory vpc9)

Xpose command: `xpose.VPC (vpc.info="vpcx/vpc_results.csv", vpctab= "vpcx/vpctabx", PI="NULL", by="STRT", PI.ci="area", PI.real=TRUE, type="n")`

* Home work