**IPRED versus DV**

Often simulated individual predictions (IPRED; i.e., those without RUV) are used when establishing an individual profile. This is because any decisions we may make for that individual should ideally be based on the underlying process and in the absence of the observed variable’s (i.e., ANC) random noise/measurement error or random intra-individual variability.

In your model, there is no physiological or pharmacological process that explains why individual ANC profiles bounce up and down. This is shown by the smooth curve in this time-period when you simulate IPRED or population predicted (PRED) from your model.

The ANC fluctuations you see when you simulate DV, are due to the residual error model and simulated ERR terms that are added to IPRED to make DV. Therefore, any fluctuations you see are random and more due to measurement error rather than individual’s underlying ANC profile.

This is one reason why our durations in severe neutropenia appear to be different. In the Shiny app, I’ve used PRED for the line to represent the “average” and used IPREDs for the 95% prediction intervals. I did not use DV, because we want to capture a range of ANC profiles that are likely to occur in an individual, and not the ANC profiles that are likely to be measured in an individual – as we know, assays and assessments have error which is then measured.

Scenarios you would need to simulate DVs to capture the range of profiles likely to be measured include; clinical trial simulation – which this is not – or for a VPC.

I would recommend using simulations of IPRED.

**PRED versus mean**

The PRED ANC profile for the model already provides a nice summary as to the average or “typical” profile for an individual with *x* covariates. It may not be average as in a “mean” or “median” sense – but it is the “most likely average” as estimated by maximum likelihood estimation. As this is the “average” for *x* covariate profile, you do not need to calculate the mean or median of the simulations as simulated inter-individual variability is essentially centred about the PRED. However, it is appropriate to calculate the median when the simulation study contains mixed covariate groups as each of these different covariate groups will have a different PRED.

This is another reason why our results are different. No matter how many simulations are performed, PRED will always be the same as it is not subject to random effects, but 95% prediction intervals based on IPRED will slightly differ as the random number generator may spit out different ETA values every time when given a different seed. The mean, however, is much more dependent on the number of simulations – you might find that if you performed a few studies with varying numbers of simulations and seeds, you will get different values for the mean, but the PRED would be the same every time.

I would recommend using PRED for summarising the “average.”

**Prediction versus Confidence Intervals**

Commonly we use prediction intervals (percentiles) as the confidence interval method assumes that the data is normally distributed and that the mean is the centre of the distribution.

**Methods for calculating duration in severe neutropenia**

The method that I used for calculating the duration in severe neutropenia in the Shiny app is based on the PRED, and the 95% prediction intervals are from the IPRED.

I think the differences in our results come from the prediction/summary statistics that we have used to calculate the duration in severe neutropenia, rather than the actual method to do so.

The method that you have used, however, assumes that in the 24-hour interval where an individual enters or exits Grade 4 neutropenia, the slope of change in ANC is linear – which it is not – and therefore this method can only provide an approximation. This method would also be quite exhaustive if written into R.

I’ve attached a NONMEM control stream of your model, with an extra compartment added that collects the duration each individual spends in Grade 4 neutropenia. You’ll find that it only requires an extra 3 lines of code and uses differential equations.

100sims_PRED_versus_Mean.pdf