Details of Population PK-VK Scenario

The structure of the PK-VK model was as follows:

$$\begin{aligned} \frac{\partial I}{\partial t} &= V \cdot T - \delta \cdot I \\ \frac{\partial V}{\partial t} &= (1-\varepsilon) \cdot I - c \cdot V \end{aligned}$$

I, t, V, T, δ, ε and c represent infected cells, time (days), virus, density of target cells, second phase slope of viral decline, constant drug effectiveness and rate at which virions are cleared, respectively. For simulation, for c, δ and ε were set to 13.4, 0.58 and 0.999, respectively. A between-subject variance of 0.0625 was set for c and δ. T was declared as $c \cdot \delta$. ε was fixed to 0.999. Residual standard deviation (additive on the log10 scale) was set to 0.19. Full details are presented elsewhere [1].

For the VPC, observed data below the LLOD were imputed post hoc in R using the following procedure, which is based on established methods for normalized prediction distribution errors [2]:

1. For individual i at measurement j, draw a random uniform number $u_{ij} \sim U(0, p_{ij,<\text{LLOD}})$, where $p_{ij,<\text{LLOD}}$ is the probability of the observation for individual i at measurement j is below the LLOD. This probability is generated by NONMEM in the "PRED" column for observations flagged as LLOD when using the M3 method.

2. Compute the inverse of the cumulative probability distribution (assuming $N(0,1)$; i.e., standard normal) of u_{ij}, $\phi^{-1}(u_{ij})$. This can be done since $p_{ij,<\text{LLOD}}$ is the cumulative distribution function of $(\text{LLOD} - \mu_{ij})/\sigma$, where μ_{ij} is the individual (i) predicted mean at measurement j and σ is the residual standard deviation (both estimated in NONMEM).

Hence, this ratio is "standardized" by subtracting the mean and dividing by the standard deviation (i.e., standard normal).

3. From first principles, $\phi^{-1}(u_{ij})$ is a z-statistic, where $z = (y_{ij} - \mu_{ij})/\sigma$. Since μ_{ij} and σ are known from the model (i.e., outputted in NONMEM), the imputed y_{ij} is $\phi^{-1}(u_{ij}) \cdot \sigma + \mu_{ij}$.

The R code for this imputation is provided in the Supplementary Material.

References

[1] Laouenan C, Guedj J and Mentre F. Clinical trial simulation to evaluate power to compare the antiviral effectiveness of two hepatitis C protease inhibitors using nonlinear mixed effect models: a viral kinetic approach. BMC Med Res Methodol 2013, 13:60

[2] Nguyen THT, Comets E, Mentre F. Extension of NPDE for evaluation of nonlinear mixed effect models in presence of data below the quantification limit with applications to HIV dynamic model. J Pharmacokinet Pharmacodyn 2012, 39(5): 499-518.