Optimised blood sampling for TDM

D-optimality concepts have been used across different therapeutic areas as a tool to improve parameter precision. This represents an important advantage when sparse sampling is performed for the purpose of population pharmacokinetic modelling. Here three *D-optimised* scenarios were considered, in which 1, 2, or 3 time points were optimised for the estimation of individual CL, as predicted by the model, based only on covariate information and not on EBEs. Data analysis was performed using the PFIM software to maximise the approximation of the Bayesian Fisher information matrix[1-3]:

$$M_{BF}(\xi)^{\infty} = H^T F(\theta,\xi)^T \sum(\theta,\xi)^{-1} F(\theta,\xi) H + \Omega^{-1} \quad (6)$$

where $H = diag(\theta_1, \ldots, \theta_p)$, $F(\theta,\xi) = \frac{\partial f(\theta,\xi)}{\partial \theta^T}$, and ξ are sampling times $t_1, \ldots, t_n$ with the constraint that only sample times were allowed to be taken between 0.5 and 12 hours after dose, at discrete points each half hour, resulting in a total of 24 possible sampling time points. Samples obtained by D-optimality were then used in the simulation scenarios. Once sampling times were identified, simulations of concentrations were performed, which were then used to estimate EBEs of CL_i as performed for the *individualised* dosing scenarios described previously. The difference between the *individualised* and *D-optimised* dosing scenarios reflects the impact of D-optimal design on the precision of individual clearance estimates.

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