Robust fitting of pharmacokinetic models to Phase II/III clinical trial data

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Introduction

Pharmacokinetic analysis of Phase II/III trial data is often hampered by uncertainties in the data. This is not so much due to errors in the observations, but more so in the non-compliance to the planned doses and the incorrect recording of dose and sampling events.

Ignoring these uncertainties can result in biased parameter estimates. This is because the underlying distribution of residual errors may strongly depart from the normal distribution assumed in the likelihood function used in most population PK data analyses. Various approaches have been proposed to overcome this issue, including the modelling of non-compliance and development of accurate ways to record dose events.

Methods

An alternative way to reduce the influence of the uncertainties in the dosage times is by reversing the viewpoint. This considers the observations that are remote from the results of the individual model predictions as being indicators of a mismatch between assumed and applied dosage time. By allowing a separate additive residual error for these observations, their influence on the estimated parameters is reduced, thus improving the statistical inference. This approach is comparable to the concept used in robust regression techniques. An iterative procedure is proposed for identifying the remote observations using outlier criteria and refitting the model, until a robust regression on the individual predictions and the observations converges to the unity line.

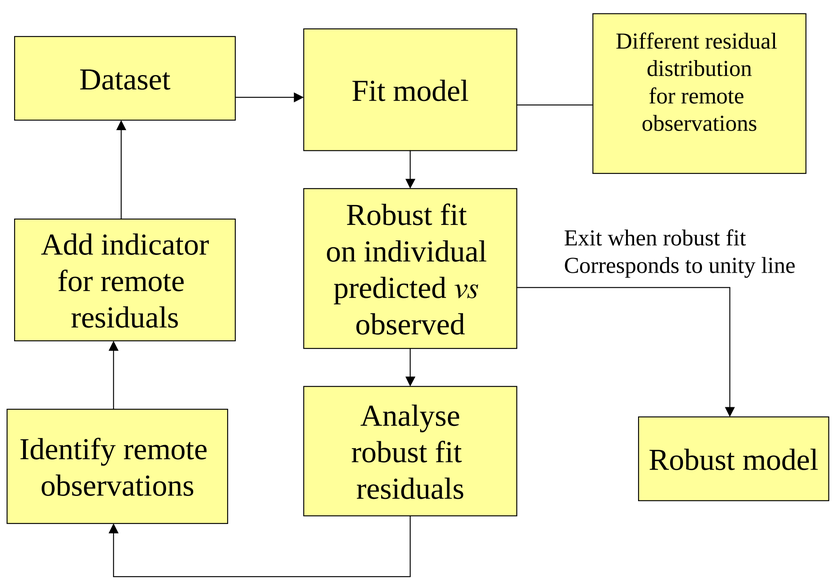

Figure 1 *Flow chart of the proposed iterative procedure of fitting PK models to data with large uncertainty about the dosage time.*

Simulation

A sparse dataset was simulated using a one-compartment model with linear absorption from a dose compartment and linear elimination from the central compartment. The forcing condition was a series of 48 dosages following a once daily regimen. One sample was taken after 24 days and one sample was taken after the last dose. The simulated data set includes 300 individuals. See for the model parameters Table 1. Software used consisted of NONMEM V v1.1 and S+ v6.2.

The following assumptions were made on the deviation of the real time from the planned dosing and sampling times:

1. A random uniform deviation in the interval –2 to 2 hours from the planned dosing time.
2. A 10% probability of skipping a dose.
3. A 10% probability of being 24 hrs late for the last visit and also taking the last dose 24 hrs late.

The simulated data were analyzed in four different ways:

1. Using the original model and the actual dosage time.
2. Using the original model and the planned dosage time (failed).
3. Using a simplified model with one stochast less and the planned dosage time.
4. Using the simplified model employing the proposed iterative procedure that reduces the influence of the concentrations that are remote from the individually predicted concentrations. Four itererations were performed, identifying the remote observation using the following criteria:

$$y_{ij} / \hat{y}_{ij} > 1.3 \vee y_{ij} / \hat{y}_{ij} < 0.76$$

Results are displayed in Table 1 (Estimated parameter values), Figure 2 (Population predicted *versus* simulated concentrations), and Figure 3 (Predictions of concentration-time profiles).

Results

Parameter	Original	Model 1	Model 3	Model 4
K_a	0.9	0.98 (5.2)	1.2 (18)	1.2 (13)
median k	0.1	0.10 (2.5)	0.038 (17)	0.070 (5.5)
median V	25	26 (3.6)	70 (16)	34 (6.0)
variance (ln k)	0.1	0.078 (13)	-	-
variance (ln V)	0.2	0.21 (9.5)	0.28 (13)	0.23 (8.3)
σ^2 multiplicative error	0.02	0.021 (11)	0.25 (13)	0.025 (22)
σ^2 additive error	0.25	0.084 (29)	1.5e5 (29)	-
σ^2 additive error EROs	-	-	-	1.4e6 (15)
-2LL	-	7815	8938	8801

Table 1 *Original parameters used in simulation model and estimated parameters (with standard errors presented as %CV) from the simulated data (Model 2 could not be optimized on the data)*

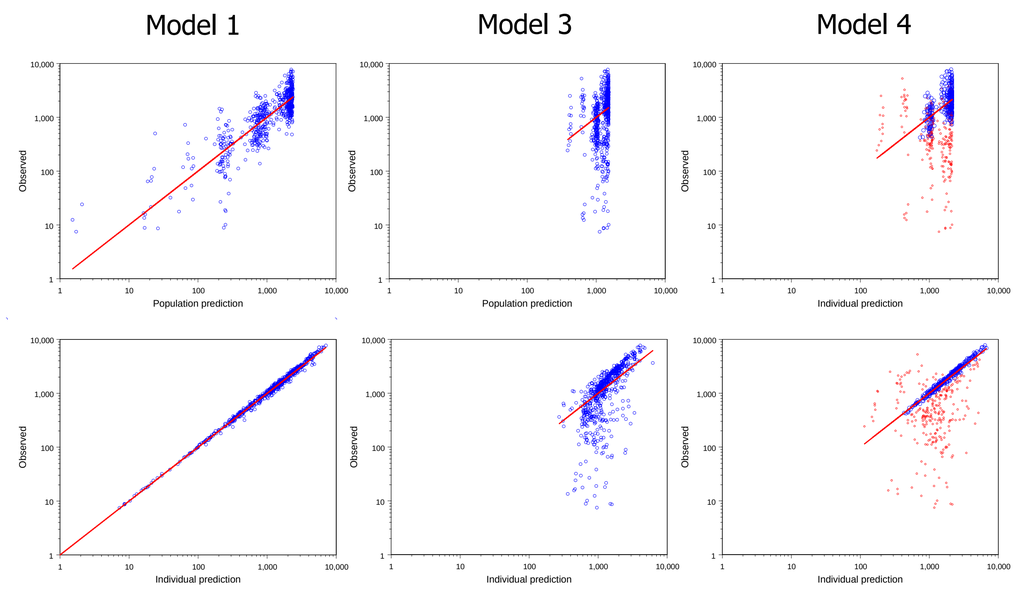

Figure 2 *Predicted versus observed concentrations for the fitted models (Red dots represent observations which were selected as remote observations; at the last iteration 42% of the observations were regarded as remote. The unity line is in red)*

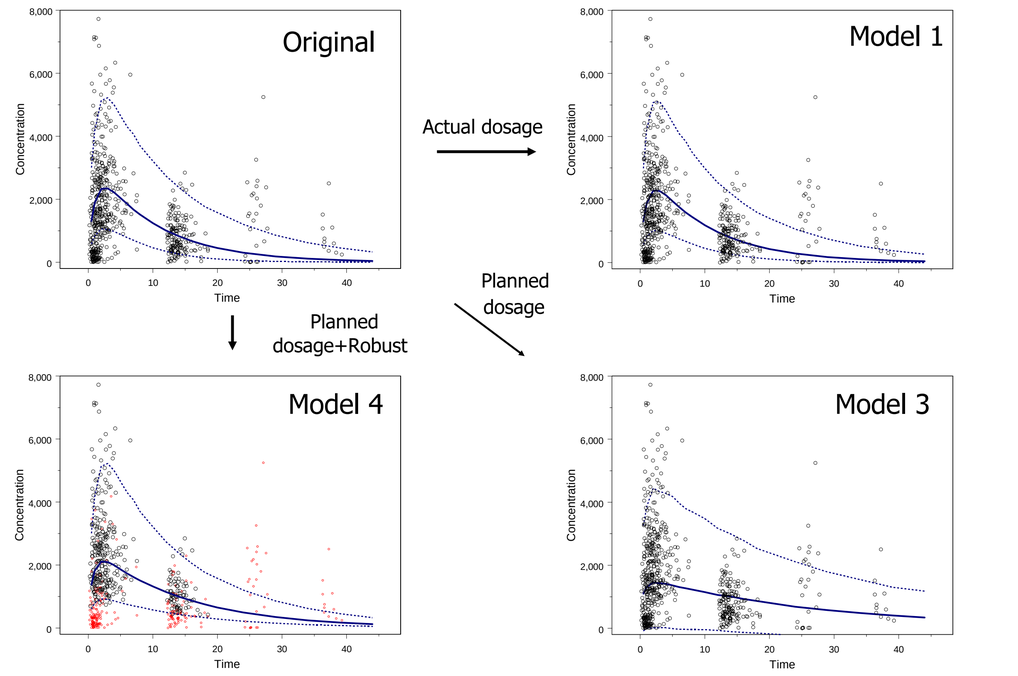

Figure 3 *Predicted and observed concentrations versus time since last (planned) dose for the original and the fitted models (Red dots represent observations which were selected as remote observations; at the last iteration 42% of the observations were regarded as remote). The lines represent the median prediction (solid line) and the 90% total variability.*

Discussion and Conclusions

Table 1 shows that the analysis of the data using the original dosage times (Model 1) provides an adequate estimate of the parameters. Also, diagnostic plots show a central position of the individual as well as the population unity line (Figure 2). The population predictions resemble those of the original model (Figure 3). When the planned dosage time is used, the full model (Model 2) cannot be optimized on the data. Analyzing the data with the reduced model (Model 3) provides strongly biased estimates of the parameters. Diagnostics shows that the observations are not uniformly distributed along the unity line. The population predictions confirm a very flat PK profile with overestimated variability during washout. When the robust fitting technique is applied, remote observations have less influence on the parameter optimization, which improves the inference, diagnostics and predicted variability of the population concentration-time curves (Model 4). Nevertheless, some deviations from the original remains, which suggests that effort to exactly record the actual dosage time is imperative.

It is concluded that the use of a robust fitting technique improves the inference when optimizing PK models on phase II/III data with outliers due to incorrect recording of dosing and sampling time.

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