Sufficiently high observation density justifies a sequential modeling approach of PKPD and dropout data

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Background

- A common approach to modeling the exposure-dependent efficacy or safety outcome of a clinical trial is to first develop a model describing the pharmacokinetics (**PK: CP, concentration**) of the drug, and subsequently explaining the observed efficacy using the mean or individually predicted PK as an independent variable in a pharmacodynamic (**PD: PI, pain intensity**) model.
- A similar sequential approach may be used in the construction of hazard models for describing observed dropout, where the predicted PKPD is used to drive the hazard model.
- Unless the hazard is described using observed data only, the sequential approach to modeling the hazard is theoretically less preferable to a simultaneous approach where PKPD and hazard model parameters are estimated jointly.
- Here, we investigate if sequential and simultaneous approaches result in similar parameter estimates for six simulated study scenarios with varying density of PKPD data.

Methods

- The data for this study was simulated using a one-compartment PK model and an inhibitory PD model describing the effect (PI) using parameter IC50.
- Dropout was simulated using a hazard proportional to the efficacy: HAZ=A*PI.
- The hazard of dropping out was estimated using a random dropout model (**RD**, [2]) based on observed PI only, and an informed dropout model (ID, [2]), that used the PD model to explain the hazard.
- The ID model was fit sequentially (**SEQ**) and simultaneously (**SIM**) with the PD data. PD and hazard model parameters were estimated for the 3 models using NONMEM.
- The joint likelihood for observing the pain intensity data (Y_O) and dropout data (T) is given by [2]:

$$P(Y_O,T)=\int P(T|Y_O,\eta)P(Y_O|\eta)P(\eta)d\eta$$

- If the conditional likelihood for the dropout data depends on the random effect, η, (as in ID models), it should be estimated simultaneously with the PD data.
- In order to investigate the error made by fitting the ID model sequentially, the deviation between estimated and true parameter estimates obtained with RD, SEQ, and SIM was derived and compared:
- Deviation = (Estimate-True)/True * 100%

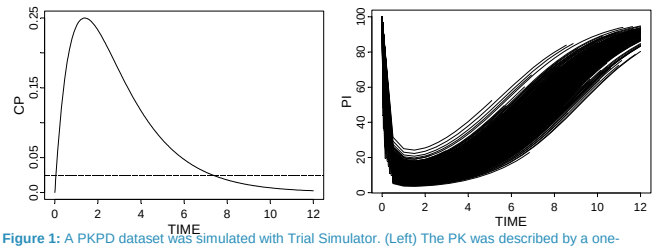

Figure 1: A PKPD dataset was simulated with Trial Simulator. (Left) The PK was described by a one-compartment model with oral absorption and the following PK parameters (no variability): KA=1, CL=10, V=20. Horizontal line shows TVIC50 of the PI model. (Right) Pain intensity following administration of a single dose of 10 at TIME=0 was described by a direct effect IMAX model:PI = 100*IC50/(CP+IC50), IC50=TVIC50*exp(IIV), with TVIC50 = 0.025 and IIV being normally distributed with mean 0 and variance 0.1 (IIV limited to -3, 3)

Models and Dataset

- Concentration (CP) and Pain Intensity (PI) was simulated in Trial Simulator using PK and PD models and parameter values defined in **Figure 1**. The hazard model used for simulating data was defined as:

  HAZ=PIHZ*PI, with PIHZ=0.005
- **6 scenarios** with increasing number of PD observations (from 2 to 24) were simulated with pain intensity observed at:
  - **1**: 0, 12 hrs
  - **2**: 0, 6, 12 hrs
  - **3**: every 4th hrs btw 0 and 12 hrs
  - **4**: every 2th hrs btw 0 and 12 hrs
  - **5**: every hr btw 0 and 12 hrs
  - **6**: every 30 mins btw 0 and 12 hrs
- 1000 subjects were simulated in each scenario, and the (true) value of ETA was saved with each simulated subject as ETA0.
- The following models were fit with datasets from each scenario: (x is the number of the scenario, from 1 to 6)

  HAZRD_10x_a: Random dropout model (RD). The parameter of the pain intensity component (ie. the individual value of IC50) was estimated independently of the dropout data. The parameter of the hazard component (PIHZ) was estimated based on observed pain intensity, and information about dropout time or censoring. The estimated value of IIV was saved with the results as ETA1, and the result file was used as input file in the HAZIDSIM_10x_a and HAZIDSEQ_10x_a models, see **Table 1**.

  HAZIDSIM_10x_a: The parameters of the PD and dropout models were estimated simultaneously (SIM). The individual values of ETA were saved with the results as ETA2

  HAZIDSEQ_10x_a: The value of ETA1 was input from the dataset and used to define the parameter of the pain intensity component. The dropout model was estimated using the corresponding predicted PI in a sequential analysis (SEQ).

SCEN	ID	TIME	DRPO	DV	DV0	ETA1	TYPE	ETA0
1	1	0	0	89.56	89.56	0.00	1.00	-0.85
1	1	8.51	1	0.00	89.56	0.00	2.00	-0.85
1	2	0	0	91.50	91.50	0.00	1.00	-0.21
1	2	4.8	1	0.00	91.50	0.00	2.00	-0.21
...	...	...	...	...	...	...	...	...
6	996	6.5	0	32.28	18.79	-0.52	1.00	-0.43
6	996	7	0	25.52	32.28	-0.52	1.00	-0.43
6	996	7.5	0	44.70	25.52	-0.52	1.00	-0.43
6	996	7.96	1	0.00	44.70	-0.52	2.00	-0.43
...	...	...	...	...	...	...	...	...

Table 1: NONMEM dataset

SCEN: Scenario (1-6), **ID**: Subject Identifier, **TIME**: Time, **DRPO**: Right-censored = 0, Dropped out = 1, **DV**: Observed PI from current record, **DV0**: Observed PI from previous record, **ETA1**: ETA estimated with SEQ, **TYPE**: PI = 1, Dropout = 2, **ETA0**: True, simulated ETA

Results And Discussion

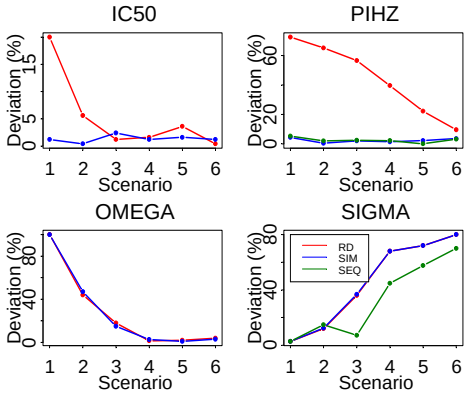

Figure 2: Absolute deviation of the four estimated parameters for each of the six scenarios. IC50 and OMEGA are not estimated in the sequential (SEQ, green curve) models.

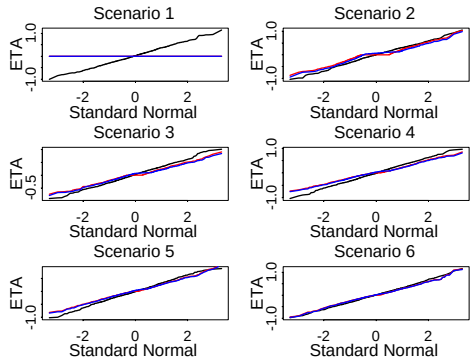

Figure 3: QQ-plots of ETAs from the RD (red) and SIM (blue) models compared to the true, simulated value (black).

If dropout depends on pain, then it is safe to assume that the dropout data contains information about the true PI.

Therefore, it is not surprising that the estimate of the PI model parameter, IC50, may be influenced by the hazard model (in addition to the observed PI for a non-constant PI). As the frequency of PI assessments increases, the influence of dropout on the estimate of IC50 decreases.

Figure 2 (upper left) shows that increasing density of PI measurements leads to increasing precision in the RD model, while the information from the dropout data "spills over" and supports the estimation of IC50 in the SIM model. Hence IC50 is well estimated in all scenarios for the SIM model.

Figure 2 (upper right) shows that the PIHZ parameter is well estimated in all scenarios with SIM and SEQ that rely on unobserved data, ie. the underlying pain intensity model. Relying only on observed data (RD model) leads to an inaccurate estimate in the sparse scenarios. In scenario 6, the precision of the estimate of PIHZ is almost as good with RD as with SEQ and SIM.

Unlike for the IC50, the dropout data does not seem to support the estimation of the interindividual variability (**Fig. 2, lower left**), which is estimated with similar precision using the RD and SIM models.

Interestingly, the precision of the estimate of SIGMA decreases as the frequency of pain intensity observation increases (**Fig. 2, lower right**)

Figure 3 shows the individual parameters (ETA) from the RD (red) and SIM (blue) models compared to the true value simulated with Trial Simulator (black). While the data is too sparse to establish individual parameters in the first scenario (where only one pain intensity measurement is recorded), ETAs are estimated with reasonably good precision in the remaining five scenarios.

Conclusion

- The hazard model parameter was well described in all six scenarios with either of the SIM and SEQ models.
- The benefit of the joint analysis was a reduction in deviation of PD model parameter in sparse scenarios where the underlying PI had considerable fluctuations between observations.
- The benefit of a the sequential analysis was a simplification of models and datasets, and decreased model runtime.
- While the conclusion that sufficient density in the observed PD data allows for a sequential analysis holds for the present simulated dataset, other models and datasets require individual consideration (and simulation-based diagnostics) in order to determine if a sequential analysis may be used or if a joint analysis should be conducted.

Rerences

[1] Diderichsen et al.: Modeling "Pain Memory" is Central to Characterizing the Hazard of Dropping Out in Acute Pain Studies, ACOP 2009 (poster)

[2] Hu and Sale: A Joint Model for Nonlinear Longitudinal Data with Informative Dropout, J Pharmacokinetics and Pharmacodynamics, 30, 2003

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