A comparison of sequential and joint fitting of pain intensity and dropout hazard in acute pain studies

Paul Matthias Diderichsen[1], Sandeep Dutta[2]
[1]Abbott GmbH & Co. KG, Ludwigshafen, Germany – Abbott A/S, Copenhagen, Denmark
[2]Abbott Labs, Abbott Park, IL, USA

Background

- Subjects in acute pain studies not receiving adequate pain relief have a high risk of dropping out of the study. As the dropout is not completely at random, this necessitates the construction of appropriate dropout models in order to reproduce the observed data in simulation.
- Such dropout models may depend on observed pain intensity (PI) that is predicted by an underlying model.
- Initially [1], the PI and dropout models were developed sequentially, ie. a pain intensity model was developed independently of the dropout data, and then used to explain the dropout data.
- However, when dropout depends on unobserved PI (between observations of PI), the dropout and PI should theoretically be modeled simultaneously.
- The objective of this work was to compare the PI and dropout model parameter estimates obtained from fitting PI and dropout data sequentially vs. simultaneously using three classes of dropout models: Completely random dropout (**CRD**), random dropout (**RD**) and informed dropout (**ID**) models [2]. (See Box 1)

Methods

- Observed PK and PI following administration of study drug, active control, or placebo were modeled as described in [1]. In the CRD models, the risk of dropping out was modeled as a time-dependent baseline hazard. In the RD and ID models, the baseline hazard was combined with a PI-dependent term.
- Parameter values were estimated in NONMEM, using a sequential and simultaneous approach.
- The joint likelihood for observing the PI data (Y_O) and dropout data (T) is given by [2]:

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

- This implies that if the conditional likelihood for the dropout data depends on the random effect, η, it should be fit simultaneously with the PI data.
- The error made by fitting the ID model sequentially, was assessed by comparing parameter estimates and simulations from a simultaneous and sequential analysis.

Models and Dataset

- A dataset was created by enriching the dropout data with a dense set of "other-type event" records (EVID=2) for each subject and merging with PK model parameters obtained in a previous analysis [1].
- The PI model (PD_761) was fit using the dataset which was then updated with the estimated PI model parameters. This was necessary in order to ensure consistency in the PI parameter estimates between sequential and simultaneous fits of the CRD and RD models.
- By including both PK, PI, and dropout data in one file, it was possible to use the same dataset for estimating dropout model parameters for all three classes of dropout models, re-estimating the PI model, and to simulate survival curves.
- In the RD models, the observed PI was used as a covariate on the hazard, and it was therefore necessary to impute it by carrying forward the most recent PI observation to the following EVID=2 records.

Results And Discussion

Estimate (SEE)	PD_761	HAZ_313	HAZ_314	HAZ_315
OFV	NA	6554.239	6315.791	**6362.905**
POW	**0.280 (0.0766)**	0.280 (0.0768)	0.280 (0.0767)	**0.291 (0.0839)**
KIN	**3.62 (0.849)**	3.62 (0.851)	3.62 (0.850)	**3.50 (0.848)**
KOUT	**2.56 (0.464)**	2.56 (0.463)	2.56 (0.464)	**2.60 (0.480)**
OMEGA	**2.03 (0. 475)**	2.03 (0.475)	2.03 (0.475)	**2.10 (0.493)**
SIGMA	**186 (19.1)**	186 (19.1)	186 (19.1)	**186 (19.1)**

Table 1: Comparison of **PI model** parameter estimates when estimated using PI data only (PD_761), or simultaneously with dropout data using a CRD (HAZ_313), RD (HAZ_314), or ID (HAZ_315) model

Table 1 shows the estimated PI parameters based on the PI (only) model (PD_761), compared to the estimates from three simultaneous fits of PI and dropout data. As expected, the results from the CRD (HAZ_313) and RD (HAZ_314) models are identical to the parameter values obtained from the original PI model. The variations in standard errors may be attributed to numerical inaccuracies.

This result is not surprising since the CRD and RD dropout models do not depend on any prediction made by the PI model. Hence, there is no dependence on η in $P(T|Y_O, \eta)$, and the integral for $P(Y_O|T)$ can be separated into two factors depending on dropout and PI, respectively.

The parameter estimates from the ID model (HAZ_315) show minor differences from the estimates based on PI data only. Interestingly, the standard errors on the parameter estimates remain mostly unchanged or even increase when including the information contained in the dropout data.

The upper two and lower left panels in **Figure 1** show observed and simulated survival curves. The gray curves and gray shaded areas show the medians and 95% prediction interval based on 25 simulated trials. **Figure 1** shows that while both the RD and ID models describe the observed survival curve with good accuracy, the CRD model fails to capture the characteristics of the dropout data. The lower right panel of **Figure 1** shows the medians of the three models compared to the observed survival curve.

Considering the upper two panels in **Figure 1**, it is not surprising that the objective function (-2LL of PI and dropout data under the model) improves in the RD model compared to the CRD model. The increase in OFV observed when going from the RD to the ID model is not apparent in **Figure 1**.

Table 2 shows parameter estimates obtained from sequentially and simultaneously fitting the PI and dropout data. **Table 2a** and **Table 2b** show that the hazard model parameter estimates from the CRD and RD models are equivalent when estimated sequentially (HAZ_303, HAZ_304) and simultaneously (HAZ_313, HAZ_314) with the dropout data

Table 2c shows that allowing the dropout data to affect the PI parameter also affects the hazard model parameter estimates, which change between models HAZ_305 and HAZ_315. The standard estimates for two of the 5 model parameters are reduced.

Figure 2 shows observed and median and 95% prediction interval for 25 simulated trials based on the ID model fit sequentially (red) and simultaneously (blue) with the dropout data. As indicated by the similarity in OFV shown in Table 2c, there are only minor differences in the predictions of the two models.

Estimate (SEE)	HAZ_303	HAZ_313
BLHAZ	-3.29 (0.444)	-3.29 (0.500)
D7SS	3.28 (1.57)	3.28 (1.80)

Table 2a: Comparison of **CRD hazard model** parameter estimates.

Estimate (SEE)	HAZ_304	HAZ_314
BLHAZ	-8.05 (0.898)	-8.05 (0.918)
PIHAZ	0.0635 (0.00932)	0.0635 (0.00954)
PIIN	2.55 (1.68)	2.55 (1.72)
PIOUT	2.83 (0.892)	2.83 (0.901)
D7SS	6.33 (3.69)	6.33 (3.75)

Table 2b: Comparison of **RD hazard model** parameter estimates.

Estimate (SEE)	HAZ_305	HAZ_315
OFV	**6365.590**	**6362.905**
BLHAZ	**-7.18 (0.844)**	**-7.37 (0.804)**
PIHAZ	**0.0519 (0.00852)**	**0.0540 (0.00900)**
PIIN	**4.04 (3.02)**	**3.48 (1.96)**
PIOUT	**3.49 (1.33)**	**3.13 (0.772)**
D7SS	**7.77 (5.00)**	**8.86 (5.19)**

Table 2c: Comparison of **ID hazard model** parameter estimates.

Box 1: Models developed. All models were ADVAN6 TOL=6 with FOCE LAPLACE, except HAZ_315 which had TOL=5. In sequential models, the -2LL was given, while the likelihood was given in simultaneous models. f() is a function defining the hazard, λ. t, DV, and IPRE are time, and observed and model-predicted PI.

PD_761: PI model as described in [1].

HAZ_303: Sequential fit of PI and dropout data using a CRD model. The hazard depends on time (t). λ = f(t)

HAZ_304: Sequential fit, RD model. The hazard depends time and observed PI (DV). λ = f(t, DV)

HAZ_305: Sequential fit, ID model. The hazard depends on the model-predicted pain intensity (IPRE). λ = f(t, IPRE)

HAZ_313: Simultaneous fit, CRD model. (corresponding to HAZ_303) λ = f(t)

HAZ_314: Simultaneous fit, RD model. (corresponding to HAZ_304) λ = f(t, DV)

HAZ_315: Simultaneous fit, ID model. (corresponding to HAZ_305) λ = f(t, IPRE)

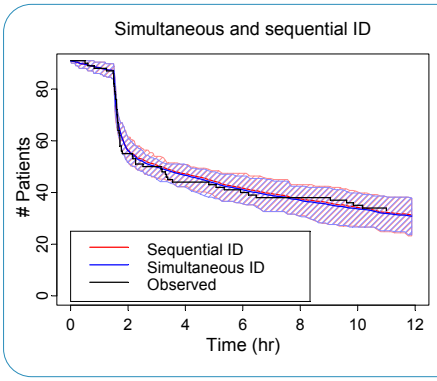

Figure 2: Median (95% prediction interval) predicted number of surviving patients based on a sequential (red, HAZ_305) and simultaneous (blue, HAZ_315) ID hazard model.

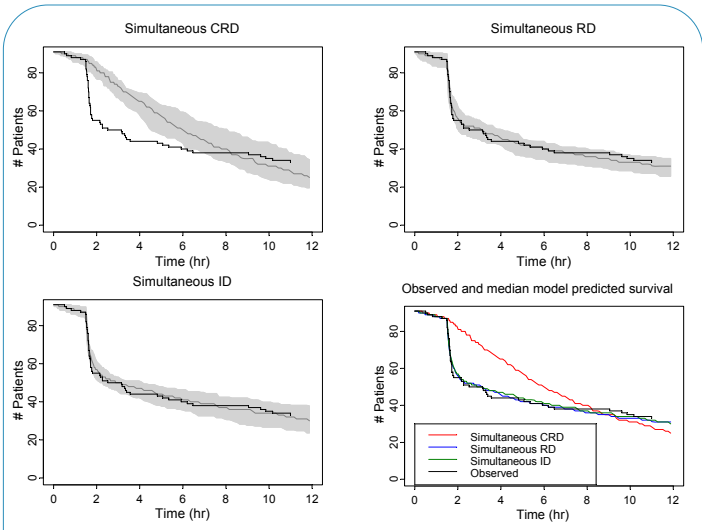

Figure 1: Observed (black) and median (95% prediction interval) predicted number of surviving patients based on CRD (upper left), RD (upper right), and ID (lower left) hazard models. Lower right: Comparison of median predicted and observed number of surviving patients.

Conclusion

- In acute pain studies where dropout can be assumed to truly depend on PI, dropout data is expected to contain information about the underlying PI. Hence simultaneous fitting of PI and dropout data is expected to improve the fit of the PI and the PI dependent hazard.
- However, in the present analysis, jointly fitting the dropout and PI data using the ID model did not provide a better fit compared to the sequential fit.
- Dropout and PI model parameter estimates changed up to 14% and 4%, respectively, when PI and dropout data were fit simultaneously instead of sequentially. However, **the survival curves simulated using the two approaches did not show any apparent difference, and both provided a good fit to the observed data**.
- The similarity in predictive performance between the sequential and simultaneous approaches is possibly due to the intensive PKPD sampling, which reduced the amount of additional pain intensity information contained in the underlying model as compared to observed data.

References

[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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