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Likelihood based approaches to handling data below the quantification limit using NONMEM VI

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Abstract *Purpose* To evaluate the likelihood-based methods for handling data below the quantification limit (BQL) using new features in NONMEM VI. *Methods* A two-compartment pharmacokinetic model with first-order absorption was chosen for investigation. Methods evaluated were: discarding BQL observations (M1), discarding BQL observations but adjusting the likelihood for the remaining data (M2), maximizing the likelihood for the data above the limit of quantification (LOQ) and treating BQL data as censored (M3), and like M3 but conditioning on the observation being greater than zero (M4). These four methods were compared using data simulated with a proportional error model. M2, M3, and M4 were also compared using data simulated from a positively truncated normal distribution. Successful terminations and bias and precision of parameter estimates were assessed. *Results* For the data simulated with a proportional error model, the overall performance was best for M3 followed by M2 and M1. M3 and M4 resulted in similar estimates in analyses without log transformation. For data simulated with the truncated normal distribution, M4 performed better than M3. *Conclusions* Analyses that maximized the likelihood of the data above the LOQ

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and treated BQL data as censored provided the most accurate and precise parameter estimates.

Keywords NONMEM VI · Limit-of-quantification · Likelihood

Introduction

How best to handle observations of drug concentration below the quantification limit (BQL) has been one of the frequently discussed questions among the community of pharmacokinetic (PK) scientists [1]. Although the ultimate solution would be having all measurements reported and/or increasing the analytical sensitivity, it is not considered to be easily achievable. Wakefield and Racine-Poon [2] and Bennett, Racine-Poon and Wakefield [3] incorporated the likelihood term for the censored measurements of an antithrombotic agent (recombinant hirudin) in a Bayesian analysis of the PK data. More recently, Stuart Beal [4] evaluated seven different methods of handling BQL observations including the likelihood-based methods in NONMEM [5]. The methods illustrated by Beal [4] can be described as follows:

- Method 1 (M1): Discard BQL observations and apply extended least squares to the remaining observations.
- Method 2 (M2): Discard BQL observations and apply the method of maximum conditional likelihood to the remaining observations.
- Method 3 (M3): Maximize the likelihood for all the data treating BQL observation as censored.
- Method 4 (M4): Like M3 but the likelihoods for data above and below the LOQ are conditioned on the observations being greater than zero.
- Method 5 (M5): Replace BQL observations with LOQ/2 and apply extended least squares estimation.
- Method 6 (M6): Replace first BQL observation with LOQ/2 and discard the rest of them as in M1.
- Method 7 (M7): Replace first BQL observation with 0 and discard the rest of them.

Beal clearly stated that M7 should not be used as it introduced the greatest bias in parameter estimates [4]. Substitution for BQL observations with a certain (non-zero) value (M5 and M6) has often been shown to give less biased parameter estimates compared to M1 or M7 [4,6,7], but it is considered to be somewhat arbitrary and less principled compared to the likelihood based approaches [4]. Also in a recent study of handling BQL data by Bergstrand et al. [8], M6 has been shown to introduce greater bias in parameter estimates than M1 in a one compartment PK example. According to Beal [4], M3 seemed to be generally better than any other method (M3 and M4 resulted in almost identical results [4]). However, his evaluation was limited to a one compartment PK model with bolus input.

In the current investigation, M1, M2, M3, and M4 were evaluated using simulations based on a two compartment PK model with first order input and proportional residual error where the parameter estimates might be more sensitive to the method of handling BQL data. M2, M3 and M4 were also compared for the case where the simulated

distribution for residual error is a truncated normal. Implementation of each method is described in an Appendix. As some features of NONMEM have been updated with the newer levels of NONMEM version, the most up-to date code was also added to that section.

Materials and methods

Part I.a. Evaluation of M1, M2, and M3

1. *Simulation* A two compartment PK model with first order oral absorption was used for simulation. The PK parameters and variabilities are provided in Table 1. The exponential error model (Eq. 1) was used for inter-individual variability (IIV) and the proportional error model (Eq. 2) was used for residual unexplained variability (RUV):

$$p_i = p \cdot \exp(\eta_i) \tag{1}$$

$$y_{ij} = f_{ij} \cdot (1 + \varepsilon_{ij}) \tag{2}$$

where p_i is the parameter for individual i, p is the typical value of parameter, y_{ij} is the j^{th} observation in the i^{th} individual, f_{ij} is the model predicted value for y_{ij}, η_i is the inter-individual random effects and ε_{ij} is the residual random effects.

If a negative dependent variable (DV) was simulated, another random error was selected until DV was greater than or equal to zero. Two sampling designs were used: 24 samples per individual (extensive design; Part I.a.1) and a reduced data set with half of the samples randomly removed resulting in about 12 samples per individual (practical design; Part I.a.2). Observations (concentrations) were simulated for 100 individuals and 100 such data sets were created using NONMEM VI 1.0 [5].

2. *Data set preparation* Four different levels of LOQ (0.2, 0.25, 0.3, and 0.4), which correspond to approximately 10%, 20%, 30%, and 40% loss of data (Tables 2 and 3), were used to evaluate each method. For M1 and M2, the missing data items

Table 1 PK parameters used for simulation

PK parameters	Mean	IIV (% CV)
CL (l/h)	30	20
VC (l)	70	20
VP (l)	200	20
Q (l/h)	20	20
KA (h^{-1})	1.5	20
RUV	15 (% CV) or 0.2 (mg/l, SD)[a]	
Dose (mg)	700	

[a] In part II, the additive error model was used for simulation

CL, clearance; VC, central volume of distribution; VP, peripheral volume of distribution; Q, inter-compartmental clearance; KA, absorption rate constant; IIV, inter-individual variability; RUV, residual unexplained variability; CV, coefficient of variation; SD, standard deviation

Table 2 Part I.a.1: The proportion of BQL data and the success rate (%) (extensive design: 24 samples/individual; log transformed data)

LOQ	BQL proportion (%)	Success rate (%)			
		All data	M1 (Discard)	M2 (YLO)	M3 (F_FLAG)
0	*0.00*	*85*			
0.2	12.9		94	84	89
0.25	21.6		92	81	84
0.3	29.9		90	71	78
0.4	42.9		47	44	61

The values obtained from the analysis using all data are in italics

Table 3 Part I.a.2: The proportion of BQL data and the success rate (%) (practical design: ∼12 samples/individual; log transformed data)

LOQ	BQL proportion (%)	Success rate (%)			
		All data	M1 (Discard)	M2 (YLO)	M3 (F_FLAG)
0	*0.00*	*63*			
0.2	12.7		79	62	69
0.25	21.4		77	55	61
0.3[a]	29.7		83	63	72
0.4[a]	42.7		61	53	72

[a] IIV (VP) was not estimated

The values obtained from the analysis using all data are in italics

(MDV's) for observations less than LOQ were set to 1 (or these data could be simply deleted from the data set). For M3, all BQL observations were retained in the data set (MDV = 0). The values for BQL observations can be any numeric values (No character variables are allowed.). A flag variable (TYPE) was created. It was used to differentiate observations above and below the LOQ.

3. *Estimation* NONMEM VI 1.0 [5] was used for estimation. The compiler was Compaq Visual Fortran v6.6 (b). Models were fitted to log transformed data using an additive error model. Conditional estimation with the LAPLACIAN option was used. This is an approximation to the true integral using a second-order Taylor expansion around the conditional estimates of the inter-individual random effects [5,9]. With M2, the likelihood for the remaining observations (above the LOQ) is normalized by the probability that the observation is above the LOQ (Eq. 1 in [4]). This adjustment step is implemented by the use of the YLO variable, available in NONMEM VI. YLO serves as a lower bound for the interval that is used for correcting the likelihood [5]. YLO was set to be equal to the log LOQ value, as log transformed data were used. A full likelihood approach M3 treats BQL observations as censored data. With this method, the likelihood for an uncensored observation is calculated the same as in the extended least square method (i.e., normal density function) but the likelihood for a BQL observation is obtained by integrating the density function from minus infinity to the LOQ, i.e., a probability that observation is indeed BQL (Eqs. 3 and 4 in [4]). YLO is not used in M3. The likelihood of the data above the LOQ does not need to be corrected since the likelihood of the data below the LOQ is included in the calculation of the objec-

tive function value. M3 could be implemented in NONMEM VI in at least two ways: with and without the F_FLAG variable. F_FLAG is an indicator variable available in NONMEM VI that allows the model to be defined by specifying a predicted value for some observations and a likelihood for others [5]. For this application, this variable is used to distinguish between the observations that are above the LOQ and those below the LOQ [5]. For the observations above the LOQ, F_FLAG was set to 0 (a prediction) whereas for the BQL observations, it was set to 1 (a likelihood). When F_FLAG is not used, the likelihoods for both the observations above and below the LOQ needed to be specified with estimation options LAPLACIAN and LIKELIHOOD. Both approaches are referred to as M3 and only the results using F_FLAG are presented in this paper. In addition, the abbreviated function, another new feature in NONMEM VI [5], can be used. This allows the user to call NONMEM's PHI function that gives the value of the cumulative density function [5] by further utilizing PHITL function to approximate it and avoids the coding for calculation of the cumulative density. With NONMEM VI 2.0, direct use of the PHI function without providing an abbreviated function will further simplify the coding. The detailed examples for implementing each method are provided in an Appendix. The absorption rate constant (KA) was constrained to be greater than alpha, a constant characterizing the distributional phase, to avoid flip-flop. When the reduced data set (practical design, ∼12 observations/subject) was used and the LOQ was 0.3 or 0.4, the IIV in peripheral volume (VP) was not estimated to reduce the frequency of unsuccessful terminations.

4. *Evaluation* Successful termination was defined as either successful minimization or termination due to rounding error with the number of significant digits being at least 2. The bias and precision in parameter estimates of successful runs were assessed as a percent mean estimation error (mee) and root mean squared estimation error (rmse), respectively. Among the two compartment PK parameters, it was expected that the terminal slope (beta) parameter (or beta half-life) is most likely to be sensitive to the way BQL values are handled; thus, estimated parameter values were used to calculate beta and mee and rmse of beta were obtained.

$$\mathrm{ee} = \frac{(\text{estimated} - \text{true})}{\text{true}} \times 100$$

$$\mathrm{mee} = \frac{1}{N}\sum_{i=1}^{N} \mathrm{ee}_i$$

$$\mathrm{rmse} = \sqrt{\frac{\sum_{i=1}^{N} \mathrm{ee}_i^2}{N}}$$

Part I.b. Evaluation of M2, M3, and M4

M4 takes into account that a measurement cannot be negative [4] and an extra adjustment step to the likelihood is used with this method. The likelihood for an observation above the LOQ is the normal density function as in M3 but is conditioned on the fact that observations can only be positive (Eq. 7 in [4]). The likelihood for a BQL observation is the integration between 0 and the LOQ, but again, is conditional on the

fact that censored observation cannot be negative (i.e. the likelihood is normalized by the integral between 0 and the positive infinity) (Eq. 8 in [4]). Since applying M4 to log transformed values does not make sense (log transformed values can be negative), untransformed data simulated in Part I.a were analyzed using M2, M3 and M4. A proportional error model was used and the estimation option was CONDITIONAL, LAPLACIAN, with INTERACTION. The INTERACTION option was necessary due to heteroscedastic residual error.

Part II. Evaluation of M2, M3, and M4 for a truncated normal distribution

Another simulation was performed with the same fixed and random effect parameters as in Part I except that an additive RUV model was used. If a negative DV was simulated, another random error was selected until DV was greater than or equal to zero. These simulations were used to compare M2, M3 and M4 when the RUV is a truncated normal.

Results

The most common reasons for unsuccessful termination were reported as an IIV parameter estimate near zero or rounding errors. But, no other systematic differences in parameter estimates between successful and unsuccessful runs were seen in this study. However, only results from successful terminations, as defined previously, were used to calculate the reported mee's and rmse's. The results from all runs can be provided as an electronic supplement upon request.

Part I.a

The successful termination rates for each LOQ and each method are provided in Tables 2 and 3. In general, the success rates decrease as LOQ increases (more BQL observations) and M1 ranks the highest followed by M3 and M2, in both extensive and practical designs. The mee's and rmse's in beta and other PK parameters calculated from the successful runs are also provided in Tables 4–7. Despite the stability of M1, parameter estimates were severely biased especially when approximately 40% of data were discarded. Also, beta was more negatively biased as LOQ increased and the same trend was observed in clearance (CL) (Tables 4 and 6). The estimates for peripheral volume of distribution (VP) and inter-compartmental clearance (Q), however, were more positively biased (Tables 4 and 6). When the likelihood for the remaining data was adjusted (M2, YLO), the parameters were more accurately and precisely estimated compared to M1 (Tables 4–7). RUV tended to be negatively biased when BQL observations were omitted (M1 and M2) but M2 resulted in less biased estimates for RUV than M1 (Tables 4 and 6). Overall, the most accurate and precise parameter estimates were obtained with M3 which uses all data (above and below the LOQ) by treating BQL data as censored observations (Tables 4–7). Not only minimal (but slightly positive) bias in the estimate of RUV was seen for this method,

Table 4 Part I.a.1: Mean estimation error (%) of parameter estimates (extensive design, log transformed data, successful termination only)

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M1	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
Beta	*−0.442*	−19.2	−3.10	−0.756	−24.8	−2.78	−0.279	−28.3	−2.86	0.270	−35.8	−6.99	0.454
CL	*1.26*	−4.88	0.381	1.12	−8.01	0.220	1.27	−10.9	−0.1566	1.35	−19.5	−2.70	1.28
VC	*4.49*	6.36	4.71	4.55	5.09	4.31	4.59	3.47	3.94	4.71	0.31	3.47	5.09
VP	*1.44*	27.7	4.59	1.68	39.0	4.70	1.21	47.5	5.43	0.540	76.8	13.1	0.64
Q	*1.04*	8.69	1.98	0.940	14.2	2.73	0.867	19.6	3.69	0.576	34.4	7.50	0.441
dKA[a]	*4.01*	12.0	5.34	4.73	7.11	3.31	4.78	1.24	2.42	4.97	−10.5	−0.790	6.05
IIV (CL)	*−0.623*	−15.7	−1.61	−0.682	−13.4	−1.47	0.276	−6.76	−1.09	0.585	72.5	1.03	2.77
IIV (VC)	*−27.1*	−25.6	−26.4	−25.3	−27.4	−27.1	−25.9	−28.1	−28.2	−26.4	−30.0	−27.3	−26.3
IIV (VP)	*−0.136*	96.5	4.09	−2.92	85.8	2.79	−6.15	43.8	10.1	−8.61	−24.9	40.4	14.4
IIV (Q)	*−6.71*	−39.7	−12.9	−6.20	−45.8	−14.6	−5.82	−48.5	−16.2	−4.85	−49.3	−21.9	−5.04
IIV (dKA)	*115*	122	116	105	144	124	112	165	125	113	213	207	104
RUV	*−4.22*	−11.6	−6.68	4.29	−13.3	−6.53	3.25	−13.7	−5.87	2.78	−13.3	−5.12	3.39

[a] dKA = KA (absorption rate constant)—alpha

The values obtained from the analysis using all data are in italics

Table 5 Part I.a.1: Root mean squared estimation error (%) of parameter estimates (extensive design, log transformed data, successful termination only)

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M1	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
Beta	*2.98*	19.4	5.24	3.50	25.0	5.99	3.67	28.6	7.67	4.33	37.9	15.7	7.76
CL	*2.67*	5.29	2.50	2.63	8.32	2.70	2.71	11.1	2.99	2.85	23.2	5.12	3.38
VC	*5.56*	7.12	5.85	5.57	6.04	5.57	5.66	4.92	5.50	5.83	4.51	6.83	6.40
VP	*2.96*	28.1	6.38	3.62	39.6	7.38	3.70	48.2	9.94	4.29	115	22.1	8.40
Q	*2.53*	8.98	3.00	2.44	14.4	3.75	2.48	19.8	4.93	2.58	38.3	9.04	3.33
dKA	*12.0*	16.5	13.2	12.2	13.6	12.5	12.4	12.5	12.6	13.1	19.8	20.5	13.8
IIV (CL)	*13.8*	20.7	14.4	14.2	19.3	14.5	14.3	16.3	14.2	14.6	433	17.7	15.4
IIV (VC)	*30.6*	29.5	30.4	29.5	30.9	30.6	29.8	31.5	31.4	30.1	33.6	31.5	30.3
IIV (VP)	*23.1*	109	47.6	31.5	103	58.4	38.5	71.1	81.4	45.8	58.4	153	111
IIV (Q)	*16.1*	41.5	21.1	16.4	47.4	23.1	17.6	50.1	26.6	18.5	51.2	34.6	25.4
IIV (dKA)	*154*	160	157	153	178	163	155	197	158	157	250	586	142
RUV	*5.31*	12.2	7.77	5.73	13.8	7.55	5.07	14.2	7.26	5.14	14.0	7.01	6.01

The values obtained from the analysis using all data are in italics

Table 6 Part I.a.2: Mean estimation error (%) of parameter estimates (practical design, log transformed data, successful termination only)

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M1	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
Beta	*−1.25*	−18.7	−4.86	−1.36	−23.2	−6.65	−1.10	−24.6	2.13	3.09	−53.6	−1.66	5.92
CL	*1.04*	−5.07	−0.589	0.859	−8.04	−1.58	0.887	−10.4	0.265	2.13	−42.7	−3.13	2.50
VC	*4.79*	5.50	3.79	4.47	3.74	3.36	3.83	3.14	2.34	4.34	1.14	0.911	3.27
VP	*2.23*	27.2	7.34	2.50	36.5	11.2	2.57	40.9	0.443	−2.68	224	13.57	−4.78
Q	*1.03*	9.12	3.31	1.14	14.4	6.00	1.50	18.1	3.30	−1.13	67.9	10.33	−1.14
dKA	*5.35*	8.98	2.82	4.34	2.69	0.43	1.92	0.544	−3.16	4.22	−7.28	−8.54	0.300
IIV (CL)	*1.72*	−13.9	−5.31	1.19	−13.3	−4.52	−0.435	2.49	2.52	7.84	976	4.43	6.71
IIV (VC)	*−30.8*	−28.7	−30.1	−28.9	−32.1	−30.8	−29.2	−30.2	−31.1	−28.5	−31.8	−31.4	−27.8
IIV (VP)	*0.785*	81.6	32.0	2.61	43.1	41.2	4.64	N/A	N/A	N/A	N/A	N/A	N/A
IIV (Q)	*−13.6*	−50.4	−28.9	−15.2	−57.1	−34.8	−15.7	−55.5	−27.8	−8.82	−54.7	−31.6	−12.2
IIV (dKA)	*132*	129	234	117	220	122	222	216	365	151	867	667	401
RUV	*−4.41*	−10.2	−5.03	4.49	−11.8	−4.64	3.25	−10.6	−3.10	5.05	−7.85	−2.19	4.22

N/A, not available

The values obtained from the analysis using all data are in italics

Table 7 Part I.a.2: Root mean squared estimation error (%) of parameter estimates (practical design, log transformed data, successful termination only)

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods parameters	*All data*	M1	M2	M3	M1	M2	M3	M1	M2	M3	M1	M2	M3
Beta	*3.79*	19.3	8.65	5.25	23.8	12.2	6.39	26.2	10.1	7.69	62.2	21.0	12.1
CL	*2.35*	5.53	2.85	2.42	8.47	3.84	2.76	11.0	3.15	3.33	55.6	9.93	3.94
VC	*6.21*	7.02	6.43	6.03	6.27	6.23	6.04	6.33	7.49	6.76	9.93	8.81	8.22
VP	*4.35*	28.4	10.6	6.19	37.7	16.5	6.71	44.2	10.0	7.22	327	49.5	10.3
Q	*3.19*	9.68	4.69	3.29	14.9	7.23	3.91	18.6	5.23	3.49	83.3	15.7	4.42
dKA	*14.7*	17.5	20.9	14.2	19.1	19.0	18.4	20.9	26.5	18.5	38.9	34.7	27.6
IIV (CL)	*17.1*	23.7	18.0	17.9	22.7	18.6	17.1	18.2	18.7	20.1	1,894	25.4	20.8
IIV (VC)	*34.1*	32.4	33.4	32.8	35.1	34.1	33.3	34.1	34.9	32.4	36.2	35.8	32.6
IIV (VP)	*33.8*	106	72.6	65.1	82.3	106	60.8	N/A	N/A	N/A	N/A	N/A	N/A
IIV (Q)	*24.1*	53.1	35.4	25.6	59.3	41.5	27.1	58.1	38.0	26.3	58.9	47.0	31.8
IIV (dKA)	*186*	197	962	184	627	204	833	633	1,235	455	2,416	1,969	1,427
RUV	*6.32*	11.3	7.58	7.24	12.9	7.75	5.07	12.0	7.66	8.33	10.6	8.29	8.89

The values obtained from the analysis using all data are in italics

Table 8 Part I.b: The proportion of BQL data and the success rate (%) (extensive design: 24 samples/individual; untransformed data)

LOQ	BQL proportion (%)	Success rate (%)			
		All data	M2 (YLO)	M3 (F_FLAG)	M4 (F_FLAG)
0	*0.00*	*80*			
0.2	12.9		90	92	86
0.25	21.6		93	90	82
0.3	29.9		88	93	85
0.4	42.9		80	83	82

The values obtained from the analysis using all data are in italics

but the estimates for other fixed and random effects parameters were also generally better for M3 compared to M1 or M2 (Tables 4 and 6). However, the improvement achieved by M3 over M2 was not as great as the one for M2 over M1 (Tables 4 and 6).

Part I.b

When the same data as in Part 1.a were analyzed without log transformation using M2, M3, and M4, the performances were comparable. M1 was also fitted to the untransformed data but its estimates were still severely biased as in Part I.a and the results are not presented. M4 tended to be less stable than M2 or M3 (Table 8). M3 and M4 resulted in similar estimates but analyses using M4 required much longer computing times than did M3. M2 estimates were quite acceptable or slightly better for some parameters (Tables 9 and 10). Unlike analyzing log transformed data, negatively biased estimates of RUV were obtained with M3 (Tables 4, 6, and 9).

Part II

For the analysis of data simulated with a truncated normal error, M3 seemed to be most stable (Table 11) but its behavior was different from M2 or M4. In other words, the lower the LOQ, the poorer M3 performed (Tables 12 and 13), which is opposite to the trend observed for M3 in Part I and for other methods. As the LOQ decreases, beta and CL are more negatively biased whereas VP and Q are more positively biased (Table 12). The performance of M4 was generally better for the estimation of fixed effect parameters than that of M2 or M3 and consistent across the values of LOQ (Tables 12 and 13).

Discussion

Currently, the most common way to handle BQL observations is to exclude them. Although this method is simple and shown to give less biased estimates than replacing them with zero [4], it could be problematic as the remaining observations are

Table 9 Part I.b: Mean estimation error (%) of parameter estimates (extensive design, untransformed data, successful termination only)

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M2	M3	M4	M2	M3	M4	M2	M3	M4	M2	M3	M4
Beta	*−0.462*	−4.35	−7.94	−8.71	−5.57	−5.36	−6.16	−7.52	0.225	−0.246	−10.8	13.5	13.0
CL	*0.0978*	−1.03	−2.18	−2.63	−1.71	−1.99	−2.11	−2.59	−0.534	−0.761	−4.92	2.99	2.91
VC	*3.32*	3.98	3.83	3.82	3.56	2.84	2.43	3.22	1.95	1.86	2.25	2.21	1.98
VP	*0.219*	4.83	9.43	10.2	6.74	6.42	7.51	9.88	0.132	0.644	16.9	−13.1	−12.6
Q	*−0.244*	1.12	2.60	2.65	2.34	2.53	2.83	4.13	1.04	1.25	8.49	−3.94	−3.91
dKA	*4.55*	7.81	7.11	7.49	5.93	3.78	2.48	4.25	0.0369	−0.0639	0.596	0.763	0.297
IIV (CL)	*−0.995*	−4.14	−4.11	−5.22	−4.23	1.97	1.48	−4.77	6.71	6.23	−1.45	8.93	9.93
IIV (VC)	*−26.0*	−24.2	−25.0	−25.8	−25.6	−24.8	−26.7	−26.5	−25.0	−25.3	−25.3	−23.6	−23.6
IIV (VP)	*0.253*	13.9	18.6	26.3	29.2	−3.53	3.49	33.0	−25.0	−21.8	20.3	−25.4	−17.4
IIV (Q)	*−5.39*	−14.1	−19.6	−19.9	−18.7	−10.5	−10.8	−22.9	4.83	4.50	−27.3	39.9	41.5
IIV (dKA)	*91.1*	76.9	98.7	125	79.9	108	133	90.4	123	137	85.6	96.1	101
RUV	*−9.85*	−8.98	−6.64	−11.1	−8.59	−9.96	−14.8	−7.91	−12.9	−17.1	−7.35	−15.5	−17.4

The values obtained from the analysis using all data are in italics

Table 10 Part I.b: Root mean squared estimation error (%) of parameter estimates (extensive design, untransformed data, successful termination only)

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M2	M3	M4	M2	M3	M4	M2	M3	M4	M2	M3	M4
Beta	*2.93*	5.84	8.72	9.43	7.41	6.84	7.36	9.59	5.12	5.13	16.0	16.0	15.7
CL	*2.34*	2.59	3.09	3.52	3.01	3.21	3.23	3.78	2.79	2.82	6.46	4.44	4.33
VC	*4.48*	5.04	4.92	4.94	4.84	4.20	3.91	4.71	3.86	3.72	4.79	4.13	4.29
VP	*2.59*	6.39	10.3	11.0	8.70	7.79	8.69	12.3	4.69	4.73	23.7	14.6	14.3
Q	*2.22*	2.43	3.32	3.32	3.37	3.37	3.69	5.04	2.67	2.77	9.89	4.99	4.99
dKA	*11.4*	13.6	13.1	13.3	13.0	11.5	11.4	12.4	11.9	11.9	14.6	12.2	13.3
IIV (CL)	*13.6*	14.6	14.5	14.4	14.9	14.5	14.6	15.4	16.0	15.6	16.5	17.4	18.3
IIV (VC)	*30.2*	28.8	29.3	30.0	29.6	29.3	30.4	30.1	29.4	29.7	29.4	28.3	28.1
IIV (VP)	*23.3*	46.5	43.3	46.9	65.9	40.7	40.8	80.3	45.2	44.7	100	62.6	70.2
IIV (Q)	*16.6*	21.4	25.1	25.0	25.6	19.7	19.6	29.9	20.5	21.3	36.1	49.1	50.7
IIV (dKA)	*148*	141	159	170	145	166	185	149	182	194	158	163	168
RUV	*10.2*	9.79	7.49	11.6	9.34	10.5	15.2	8.99	13.4	17.4	8.74	15.9	17.7

The values obtained from the analysis using all data are in italics

Table 11 Part II: The proportion of BQL data and the success rate (%)

LOQ	BQL proportion (%)	Success rate (%)			
		All data	M2 (YLO)	M3 (F_FLAG)	M4 (F_FLAG)
0	*0.00*	*96*			
0.1	6.28		78	97	78
0.2	15.2		76	96	78
0.3	25.9		75	90	77
0.4	36.3		76	85	77

The values obtained from the analysis using all data are in italics

a biased sample [4]. This problem is illustrated in Fig. 1. If no adjustments are made to the likelihood of the remaining data (the first column of Fig. 1), the difference between the prediction made from truncated data (dashed line) and the true PK profiles (solid line) increases as the LOQ increases (i.e., more data are discarded). However, the deviations are modest when the likelihoods are adjusted (the second column of Fig. 1) or the BQL data were treated as censored observation (the third column of Fig. 1) even when about 40 % of data were discarded (LOQ = 0.4).

Although the severe bias introduced by simply excluding BQL observation (M1) could be partly corrected by adjusting the likelihood for the remaining observation (M2), it still does not use the information about the times at which the BQL values were recorded. In that sense, M3 should be a theoretically better approach than M2 and our results confirm this. As described in Methods (3. Estimation section), M3 can be implemented in different ways. If NONMEM VI is used, the new variable called F_FLAG provides a means to distinguish the observations above the LOQ (a prediction) from those below the LOQ (a likelihood). Without the F_FLAG variable, likelihoods for both the observations above and below the LOQ need to be specified under the assumption that each observation is normally distributed. In this study, both methods resulted in almost identical parameter estimates (data are not shown) except for the objective function values. In addition to the option for using F_FLAG, the normal cumulative density that needs to be obtained for BQL observations with M3 can be approximated differently. Two different approximations were tried: one is from Abramowiz and Stegun [10] and the other was obtained from the code in NONMEM subroutines PHI and PHITL. The results from the two approximations were almost identical (results are not shown).

It should be acknowledged that fitting an additive error model to log transformed data that were simulated with a proportional error model (instead of an exponential error model) involves a small model misspecification, although the difference between the two error models is expected to be very small. (Results similar to the current results were obtained for data simulated with an exponential error model in Part I.a.1; results are not shown). The proportional error model was chosen in this study as it was considered to be more realistic (similar to the nature of assay error).

Bergstrand et al. [8] observed best overall performance in M3 using the F_FLAG functionality and they reported that M3 using the likelihood for all data (without using

Table 12 Part II: Mean estimation error (%) of parameter estimates

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M2	M3	M4	M2	M3	M4	M2	M3	M4	M2	M3	M4
Beta	*−30.5*	−6.39	−25.5	−5.88	−7.30	−20.9	−5.99	−8.58	−17.1	−6.12	−13.6	−14.1	−6.08
CL	*−12.7*	−1.81	−10.1	−1.62	−2.28	−7.87	−1.59	−3.14	−6.10	−1.69	−5.26	−4.80	−1.68
VC	*3.39*	3.39	3.42	3.40	3.50	3.34	3.34	3.47	3.32	3.44	3.86	3.43	3.45
VP	*50.1*	8.30	39.4	7.26	9.96	30.6	7.46	13.9	24.0	7.54	23.2	19.2	7.80
Q	*17.6*	1.26	13.7	0.945	1.77	10.5	0.970	3.17	7.80	0.961	6.07	5.86	1.00
dKA	*7.09*	6.96	7.16	7.19	7.40	6.82	7.02	7.59	6.84	7.36	8.60	7.03	7.53
IIV (CL)	*−2.90*	−4.90	−2.41	−4.73	−4.45	−2.32	−4.38	−3.43	−3.28	−5.01	−1.19	−3.97	−5.29
IIV (VC)	*−24.1*	−23.9	−24.1	−24.3	−23.5	−24.2	−24.3	−23.5	−24.3	−24.1	−24.4	−24.2	−24.1
IIV (VP)	*80.4*	97.4	78.4	95.6	99.7	82.4	95.0	101	88.5	102	129	95.9	105
IIV (Q)	*−38.7*	−20.5	−36.3	−20.4	−22.3	−33.2	−20.7	−21.2	−30.1	−20.5	−25.2	−27.3	−21.4
IIV (dKA)	*122*	85.8	110	86.5	84.1	102	89.8	81.5	96.2	85.7	79.7	90.9	80.2
RUV	*−14.2*	1.22	−7.69	0.964	1.92	−3.26	0.950	2.37	−0.549	1.04	2.08	1.06	1.49

The values obtained from the analysis using all data are in italics

Table 13 Part II: Root mean squared estimation error (%) of parameter estimates

LOQ	*0*	0.2			0.25			0.3			0.4		
Methods Parameters	*All data*	M2	M3	M4	M2	M3	M4	M2	M3	M4	M2	M3	M4
Beta	*31.1*	12.9	26.4	11.7	14.3	22.2	11.8	18.9	18.9	11.8	23.9	16.6	12.6
CL	*13.0*	4.23	10.5	3.72	4.83	8.42	3.76	6.63	6.88	3.77	8.70	5.87	4.01
VC	*4.50*	4.47	4.50	4.43	4.62	4.45	4.37	4.71	4.45	4.48	5.08	4.46	4.48
VP	*51.6*	15.7	41.0	13.7	19.1	32.8	13.9	28.1	26.6	13.8	37.9	23.0	15.3
Q	*17.9*	3.88	14.1	3.98	4.78	11.0	3.85	7.69	8.41	3.56	10.9	6.77	3.83
dKA	*12.1*	12.3	12.1	12.2	12.7	12.0	12.1	13.3	12.0	12.4	14.2	12.1	12.5
IIV (CL)	*16.8*	15.7	16.1	14.9	15.4	16.0	14.9	16.1	15.3	15.4	17.0	15.2	15.8
IIV (VC)	*27.2*	26.9	27.1	27.4	26.8	27.1	27.3	26.7	27.2	27.2	27.5	27.2	27.1
IIV (VP)	*114*	148	114	140	145	124	138	157	126	147	187	134	151
IIV (Q)	*41.8*	30.3	39.9	30.6	33.4	37.6	30.0	35.7	35.7	29.9	37.1	34.4	31.0
IIV (dKA)	*136*	106	126	107	105	120	112	102	116	106	103	112	101
RUV	*14.6*	4.16	8.41	4.10	4.47	4.89	4.00	5.08	3.98	4.08	5.08	4.00	4.21

The values obtained from the analysis using all data are in italics

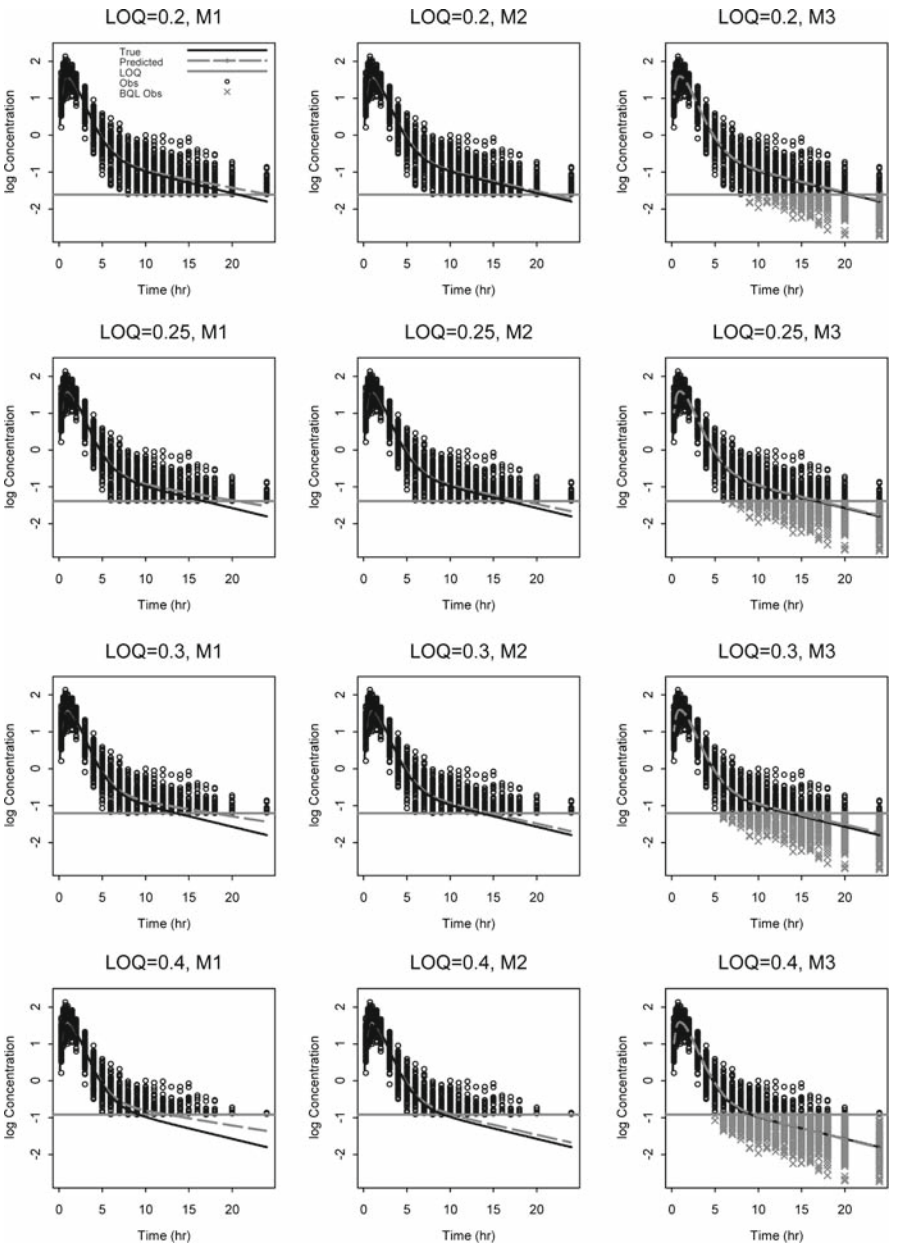

Fig. 1 Illustration of effects of different methods of handling BQL data on estimation (Plots were made from the first replicate of simulations)

F_FLAG) resulted in much lower success rates in both one compartment and two compartment models. However, in our example, we found that both methods for M3 gave rise to very similar parameter estimates and termination status.

When M2, M3, and M4 were fitted to untransformed data simulated using a proportional RUV model, the performances from these three methods were not much different. Interestingly, M4 did not show any superiority to M2 and M3 despite of its complexity and longer computation times. When the distribution of residual errors is proportional or approximately lognormal, the magnitude of residual error at the low concentrations is relatively small; thus the lack of M4 superiority might be expected.

However, when the simulated distribution is a truncated normal constrained to be positive, M4 resulted in less biased and more accurate estimates (Tables 12 and 13). With M3, the estimates became more biased as LOQ decreased, i.e., more uncensored observations are available. Without taking into account that the observations cannot be negative, the more observations that are near the LOQ values should cause CL and beta to be estimated to be less than the true values, accounting for the increase in negative bias. For VP and Q, estimates are expected to be more positively biased as more observations are available for the same reason. The likelihood for the observations with M2 is conditioned on the fact that the observation is greater than the LOQ; thus, the symptom of "poor fit with more data" was not observed with this method.

Finally, it is expected that the relationship between bias and BQL data is very complex. The fraction of BQL data was evaluated in this study and turned out to be important. However, bias is likely to be a function of several factors (for example, linear versus nonlinear kinetics, when BQL data mostly occur—absorption or distribution phase, etc.) which is difficult to completely evaluate in this type of experiment.

Conclusion

From this simulation study, it was clear that simply ignoring BQL observation (without any adjustment) can lead to severely biased parameter estimates (for example, underestimated CL and/or terminal slope; overestimated VP and/or Q), depending on the proportion of such observations. Two compartment PK with distinctive alpha and beta phases was used in this study. Results will vary depending on the model and parameter values.

If the times of the BQL observations are not available, then adjusting the likelihoods for the remaining data (M2) may improve parameter estimates compared to no adjustment (M1). M2 estimates were not best but quite comparable to those of more refined methods like M3 and/or M4. This method can also be easily implemented using YLO feature in NONMEM VI.

In most cases, the time when the BQL observations occur are recorded and a better approach for handling BQL data would be treating them as censored observation (M3). The estimates obtained with M3 and M4 were very similar for simulated data with

a proportional error model. However, M4 seems to be a preferred method when the distribution of error is truncated to be positive.

Appendix

Part I.a. Fitting an additive error model to log transformed data

Methods		M1	M2
Data	Below LOQ	`Discard or MDV=1`	`Discard or MDV=1`
	Above LOQ	`MDV=0`	`MDV=0`

Code	$ERROR (or $PRED)	`Y=LOG(F)+ERR(1)`	`CALLFL=0`
			`Y=LOG(F)+ERR(1)`
			`LOQ=xxxx`
			`YLO=LOG(LOQ)`
			`PRB=PR_Y`

	$EST	`METHOD=1 LAPLACIAN`	`METHOD=1 LAPLACIAN`

Comment(s)			`CALLFL=0 is necessary unless the route of administration is intravenous`
			
			`PR_Y for the probability of an observation being above the LOQ (optional)`

Part I.b. Fitting a proportional error model to untransformed data

Methods		M3 (with F_FLAG)	M4 (with F_FLAG)
Data	Below LOQ	`DV=arbitrary, MDV=0, TYPE=2`	`DV=arbitrary, MDV=0, TYPE=2`
	Above LOQ	`MDV=0, TYPE=1`	`MDV=0, TYPE=1`

Code	$ERROR	`SIG=THETA(.)`
		`LOQ=xxxx`
		`IPRED=F`
		`DUM=(LOQ-IPRED)/SIG`
		`ARG=ABS(DUM)`
		`W1=0.39894228`
		`W2=0.2316419`
		`B1=1.330274429`
		`B2=-1.821255978`
		`B3=1.781477937`
		`B4=-0.356563782`
		`B5=0.319381530`
		`AA=EXP(-0.5*ARG**2)`
		`R=1./(1.+W2*ARG)`
		`AUC=((((B1*R+B2)*R+B3)*R+B4)*R+B5)*R`
		`PHITL=AA*AUC*W1`
		`IF (DUM.LT.0) CUMD=PHITL`
		`IF (DUM.GT.0) CUMD=1-PHITL`
		`IF (DUM.EQ.0) CUMD=0.5`
		
		`IF (TYPE.EQ.1) THEN`
		`F_FLAG=0`
		`Y=F*(1+SIG*ERR(1))`
		`ENDIF`
		`IF (TYPE.EQ.2) THEN`
		`F_FLAG=1`
		`Y=CUMD`
		`ENDIF`
			`CALLFL=0`
			`SIG=THETA(.)`
			`LOQ=xxxx`
			`IPRED=F`
			`DUM=(LOQ-IPRED)/SIG`
			`ARG=ABS(DUM)`
			`DUM0=(0-IPRED)/SIG`
			`ARG0=ABS(DUM0)`
			`W1=0.39894228`
			`W2=0.2316419`
			`B1=1.330274429`
			`B2=-1.821255978`
			`B3=1.781477937`
			`B4=-0.356563782`
			`B5=0.319381530`
			`AA=EXP(-0.5*ARG**2)`
			`R=1./(1.+W2*ARG)`
			`AUC=((((B1*R+B2)*R+B3)*R+B4)*R+B5)*R`
			`PHITL=AA*AUC*W1`
			`IF (DUM.LT.0) CUMD=PHITL`
			`IF (DUM.GT.0) CUMD=1-PHITL`
			`IF (DUM.EQ.0) CUMD=0.5`
			`A0=EXP(-0.5*ARG0**2)`
			`R0=1./(1.+W2*ARG0)`
			`AUC0=((((B1*R0+B2)*R0+B3)*R0+B4)*R0+B5)*R0`
			`PHITL0=A0*AUC0*W1`
			`IF (DUM0.LT.0) CUMD0=PHITL0`
			`IF (DUM0.GT.0) CUMD0=1-PHITL0`
			`IF (DUM0.EQ.0) CUMD0=0.5`
			`CCUMD=(CUMD-CUMD0)/(1-CUMD0)`
			
			`IF (TYPE.EQ.1) THEN`
			`F_FLAG=0`
			`YLO=0`
			`Y=F*(1+SIG*ERR(1))`
			`ENDIF`
			`IF (TYPE.EQ.2) THEN`
			`F_FLAG=1`
			`Y=CCUMD`
			`ENDIF`

	$SIGMA	`1 FIXED`	`1 FIXED`
	$EST	`METHOD=1 INTERACTION LAPLACIAN`	`METHOD=1 INTERACTION LAPLACIAN`

Part II. Fitting an additive error model to untransformed data

Methods		M3 (without F_FLAG)	M4 (without F_FLAG)
Data	Below LOQ	DV<LOQ, MDV=0	DV<LOQ, MDV=0
	Above LOQ	MDV=0	MDV=0

Code	$ERROR	SIG=THETA(.)
		LOQ=xxxx
		PI=3.14159265
		IPRED=F
		DUM=(LOQ-IPRED)/SIG
		ARG=ABS(DUM)
		W1=0.39894228
		W2=0.2316419
		B1=1.330274429
		B2=-1.821255978
		B3=1.781477937
		B4=-0.356563782
		B5=0.319381530
		AA=EXP(-0.5*ARG**2)
		R=1./(1.+W2*ARG)
		AUC=((((B1*R+B2)*R+B3)*R+B4)*R+B5)*R
		PHITL=AA*AUC*W1
		IF (DUM.LT.0) CUMD=PHITL
		IF (DUM.GT.0) CUMD=1-PHITL
		IF (DUM.EQ.0) CUMD=0.5
		DUM1=(DV-IPRED)/SIG
		LKHD=1/SQRT(2*PI*SIG**2)*EXP(-DUM1**2/2)
		
		IF (DV.GE.LOQ) Y=LKHD
		IF (DV.LT.LOQ) Y=CUMD
			SIG=THETA(.)
			LOQ=xxxx
			PI=3.14159265
			IPRED=F
			DUM=(LOQ-IPRED)/SIG
			ARG=ABS(DUM)
			DUM0=(0-IPRED)/SIG
			ARG0=ABS(DUM0)
			W1=0.39894228
			W2=0.2316419
			B1=1.330274429
			B2=-1.821255978
			B3=1.781477937
			B4=-0.356563782
			B5=0.319381530
			AA=EXP(-0.5*ARG**2)
			R=1./(1.+W2*ARG)
			AUC=((((B1*R+B2)*R+B3)*R+B4)*R+B5)*R
			PHITL=AA*AUC*W1
			IF (DUM.LT.0) CUMD=PHITL
			IF (DUM.GT.0) CUMD=1-PHITL
			IF (DUM.EQ.0) CUMD=0.5
			A0=EXP(-0.5*ARG0**2)
			R0=1./(1.+W2*ARG0)
			AUC0=((((B1*R0+B2)*R0+B3)*R0+B4)*R0+B5)*R0
			PHITL0=A0*AUC0*W1
			IF (DUM0.LT.0) CUMD0=PHITL0
			IF (DUM0.GT.0) CUMD0=1-PHITL0
			IF (DUM0.EQ.0) CUMD0=0.5
			CCUMD=(CUMD-CUMD0)/(1-CUMD0)
			DUM1=(DV-IPRED)/SIG
			LKHD=1/SQRT(2*PI*SIG**2)*EXP(-DUM1**2/2)
			CLKHD=LKHD/(1-CUMD0)
			
			IF (DV.GE.LOQ) Y=CLKHD
			IF (DV.LT.LOQ) Y=CCUMD

Use of ABRREVIATED FUNCTION (Fitting an additive error model to untransformed data)

Methods		M3 (with F_FLAG)	M4 (with F_FLAG)
Data	Below LOQ	DV=arbitrary, MDV=0, TYPE=2	DV=arbitrary, MDV=0, TYPE=2
	Above LOQ	MDV=0, TYPE=1	MDV=0, TYPE=1
Code	$SUBROUTINES	ADVAN=4 OTHER=PHI1.for	ADVAN=4 OTHER=PHI1.for

	$ERROR	SIG=THETA(.)
		LOQ=xxxx
		IPRED=F
		VECTRA(1)=(LOQ-IPRED)/SIG
		CUMD=FUNCA(VECTRA)
		IF (TYPE.EQ.1) THEN
		F_FLAG=0
		Y=F+SIG*ERR(1)
		ENDIF
		IF (TYPE.EQ.2) THEN
		F_FLAG=1
		Y=CUMD
		ENDIF
			CALLFL=0
			SIG=THETA(.)
			LOQ=xxxx
			IPRED=F
			VECTRA(1)=(LOQ-IPRED)/SIG
			CUMD=FUNCA(VECTRA)
			VECTRA(1)=-IPRED/SIG
			CUMD0=FUNCA(VECTRA)
			CCUMD=(CUMD-CUMD0)/(1-CUMD0)
			IF (TYPE.EQ.1) THEN
			F_FLAG=0
			YLO=0
			Y=F+SIG*ERR(1)
			ENDIF
			IF (TYPE.EQ.2) THEN
			F_FLAG=1
			Y=CCUMD
			ENDIF

	$SIGMA	1 FIXED	1 FIXED
	$EST	METHOD=1 LAPLACIAN	METHOD=1 LAPLACIAN
	PHI1.for	FUNCTION FUNCA (X,X1,X2) DOUBLE PRECISION X,X1,X2,FUNCA,P5,TWO,R,E,PHI DIMENSION X(9),X1(9),X2(9,9) DATA P5/0.5/,R/.39894228037539D0/,TWO/2./ FUNCA=PHI(X(1)) E=EXP(-P5*X(1)**2) X1(1)=R*E X2(1,1)=-TWO*R*P5*X(1)*E RETURN END	

Direct Use of PHI FUNCTION (Available with NONMEM VI 2.0 beta or greater; fitting an additive error model to untransformed data)			
Methods		M3 (with F_FLAG)	M4 (with F_FLAG)
Data	Below LOQ	`DV=arbitrary, MDV=0, TYPE=2`	`DV=arbitrary, MDV=0, TYPE=2`
	Above LOQ	`MDV=0, TYPE=1`	`MDV=0, TYPE=1`
Code	$SUBROUTINES	`ADVAN=4`	`ADVAN=4`

	$ERROR	`SIG=THETA(.)`
		`LOQ=xxxx`
		`IPRED=F`
		`DUM=(LOQ-IPRED)/SIG`
		`CUMD=PHI(DUM)`
		`IF (TYPE.EQ.1) THEN`
		`F_FLAG=0`
		`Y=IPRED+SIG*ERR(1)`
		`ENDIF`
		`IF (TYPE.EQ.2) THEN`
		`F_FLAG=1`
		`Y=CUMD`
		`ENDIF`
			`SIG=THETA(.)`
			`LOQ=xxxx`
			`IPRED=F`
			`DUM=(LOQ-IPRED)/SIG`
			`CUMD=PHI(DUM)`
			`DUM0=-IPRED/SIG`
			`CUMD0=PHI(DUM0)`
			`CCUMD=(CUMD-CUMD0)/(1-CUMD0)`
			`IF (TYPE.EQ.1) THEN`
			`F_FLAG=0`
			`YLO=0`
			`Y=IPRED+SIG*ERR(1)`
			`ENDIF`
			`IF (TYPE.EQ.2) THEN`
			`F_FLAG=1`
			`Y=CCUMD`
			`ENDIF`

	$SIGMA	`1 FIXED`	`1 FIXED`
	$EST	`METHOD=1 LAPLACIAN`	`METHOD=1 LAPLACIAN`

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