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BACK-STEP METHOD FOR OBTAINING UNBIASED ESTIMATES FOR SKEWED ORDERED CATEGORICAL DATA. M.C. Persson, S. Jönsson, MSc, M.O. Karlsson, PhD, Uppsala University, Sweden.

When performing nonlinear mixed effects modelling of ordered categorical data using NONMEM, the population parameter estimates, ϕ^R, may be severely biased if data are skewed.[1] The Back-Step Method (BSM) is developed to provide less biased estimates in these situations. In BSM, data are simulated from a set of simulation parameters, ϕ^{S1}, followed by an estimation of parameters in NONMEM, resulting in estimates ϕ^{E1}. New simulation parameters, ϕ^{S2}, are calculated based on ϕ^{E1} and ϕ^R and the procedure is repeated until the difference between ϕ^R and ϕ^{E_final} is low. The assumption is that when ϕ^{E_final} are similar to ϕ^R, ϕ^{S_final} are unbiased estimates of the true parameter values. The properties of the BSM and standard NONMEM (Laplacian) methods were evaluated in Monte Carlo simulation studies. In a typical example, standard NONMEM produces 8 fold and 27 fold higher biases than BSM in fixed () and random () effect parameter estimates, respectively. BSM may thus provide an alternative when standard NONMEM estimates are biased. [1]S. Jönsson, M.O. Karlsson, 2002, Estimating Bias in Parameters for some NONMEM Models for Ordered Categorical Data, Poster no. W4228, http://www.aapspharmaceutica.com

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POPULATION PK/PD MODELING OF TESTOSTERONE (T), LH AND DIHYDROTESTOSTERONE (DHT) RESPONSE TO SINGLE SC DEGARELIX IN MALE VOLUNTEERS. U.S.H. Svensson, PhD, T. Senderovitz, MD, and M.O. Karlsson, PhD, Uppsala University, Sweden and Ferring, Denmark.

The aim was to describe the response to degarelix, a GnRH antagonist for prostate cancer using nonlinear mixed effects modeling of data from 60 subjects. Degarelix showed flip-flop PK with a long terminal half-life (47 days). A mechanism-based model for the degarelix/LH/T interaction included competitive antagonism of degarelix (estimated Ki= 0.082 ng/ml) with an endogenous agonist (EA) for GnRH receptors. Production rate of LH was linked to the fraction activated receptors through a spare receptor model (R_{50}=0.20, baseline $[EA]/[EA]_{50}$= 0.39). A continuous suppression of LH/testosterone led to receptor down-regulation, in the model estimated to a 93% decrease of receptor density at full suppression of T and a receptor mean residence time (MRT) of 4.5 days. A turn-over model described the conversion of T to dihydrotestosterone with a MRT of 6.2 hours. Through a mechanism-based model, the complex interplay could be described and potentially used for prediction.

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VALIDATION OF A NOVEL METHOD OF COMBINING BOTH CONTINUOUS AND CATEGORICAL COVARIATES IN A SINGLE JOINT FUNCTION FOR CLINICAL TRIAL SIMULATION. S. J. Tannenbaum, PhD, D. R. Mould, PhD, N. H. Holford, MB, ChB, MSc, H. Lee, MD PhD, C. C. Peck, MD, Georgetown University, Projections Research, Inc., University of Auckland, Washington, DC.

In clinical trial simulations, the standard method (STD) of creating continuous covariate vectors is to sample from a separate joint function for each categorical covariate combination. A novel method (NOV) has been developed to avoid subdividing the population. Treating all covariates as continuous, a single joint function is created from the covariance matrix and the covariate means. Non-integer values for sampled categorical covariates are transformed to discrete based on cutoff limits, defined from the inverse of the cumulative probability distribution. The purposes of this project were to qualify NOV and compare it to STD. 8 data sets of CAT (categorical, values 1 and 2) and CONT (continuous) were simulated with each combination of %CAT1=25,50, R=0.5,0.9, and CV%=20,40, where R=mean1/mean2, mean2=100, and CV is applied to each subpopulation. STD and NOV were applied to each dataset; the simulated means were compared to the original means.

% ERROR FOR subpopulation or population MEAN

			CAT1		CAT2		ALL	
%CAT1	R	CV%	STD	NOV	STD	NOV	STD	NOV
0.25	0.5	0.2	0.73	-18.57	0.11	0.42	0.24	-2.96
		0.4	0.23	-7.11	-3.98	0.41	-5.65	-1.98
	0.9	0.2	0.63	-1.44	-0.01	0.20	0.17	-0.26
		0.4	2.78	-0.14	-1.48	-0.06	-0.58	-0.16
0.75	0.5	0.2	-1.10	-5.97	0.90	11.80	-0.84	0.49
		0.4	0.27	-6.17	-3.48	12.46	-1.03	0.87
	0.9	0.2	0.54	0.95	0.73	3.88	0.54	1.81
		0.4	1.02	-3.11	0.65	2.15	0.86	-1.65

% error = 100*(original-simulated)/original

STD selects CAT then chooses CONT from the associated distribution; low R and low CV create very distinct subpopulations, so these means are better captured by STD. NOV samples both values simultaneously, so as the subpopulations overlap, either method is adequate. STD and NOV recreate the overall population means (often the demographic of real interest) equally well, and because NOV allows analysis of the whole population instead of small subsets, increasing mathematical stability and reducing workload, this can be a more useful method.