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NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.3.0
ORIGINALLY DEVELOPED BY STUART BEAL, LEWIS SHEINER, AND ALISON BOECKMANN
CURRENT DEVELOPERS ARE ROBERT BAUER, ICON DEVELOPMENT SOLUTIONS,
AND ALISON BOECKMANN. IMPLEMENTATION, EFFICIENCY, AND STANDARDIZATION
PERFORMED BY NOUS INFOSYSTEMS.

PROBLEM NO.:         1
PHENOBARBITAL IV P:ROOT F:BASE

DATA CHECKOUT RUN:              NO
DATA SET LOCATED ON UNIT NO.:    2
THIS UNIT TO BE REWOUND:        NO
NO. OF DATA RECS IN DATA SET:      744
NO. OF DATA ITEMS IN DATA SET:   8
ID DATA ITEM IS DATA ITEM NO.:   1
DEP VARIABLE IS DATA ITEM NO.:   6
MDV DATA ITEM IS DATA ITEM NO.:  7

INDICES PASSED TO SUBROUTINE PRED:
  8   2   3   0   0   0   0   0   0   0   0

LABELS FOR DATA ITEMS:
ID TIME AMT BWT APGA DV MDV EVID

(NONBLANK) LABELS FOR PRED-DEFINED ITEMS:
CL V K HALF IPRE IWRE

FORMAT FOR DATA:
(8E6.0)

TOT. NO. OF OBS RECS:      155
TOT. NO. OF INDIVIDUALS:     59

LENGTH OF THETA:   4

DEFAULT THETA BOUNDARY TEST OMITTED:   YES

OMEGA HAS BLOCK FORM:
 1
 1  1

DEFAULT OMEGA BOUNDARY TEST OMITTED:   YES

SIGMA HAS SIMPLE DIAGONAL FORM WITH DIMENSION:   1

DEFAULT SIGMA BOUNDARY TEST OMITTED:   YES

INITIAL ESTIMATE OF THETA:
LOWER BOUND    INITIAL EST    UPPER BOUND
 0.0000E+00     0.1000E-01     0.1000E+07
 0.0000E+00     0.1000E+01     0.1000E+07
 0.0000E+00     0.1000E+01     0.1000E+07
 0.0000E+00     0.1000E+00     0.1000E+07

INITIAL ESTIMATE OF OMEGA:
BLOCK SET NO.   BLOCK                                                    FIXED
       1                                                                   NO
                 0.2000E+00
                 0.1000E+00   0.2000E+00

INITIAL ESTIMATE OF SIGMA:
0.1000E+01

SIGMA CONSTRAINED TO BE THIS INITIAL ESTIMATE

COVARIANCE STEP OMITTED:        NO
EIGENVLS. PRINTED:              NO
SPECIAL COMPUTATION:            NO
COMPRESSED FORMAT:              NO
SIGDIGITS ETAHAT (SIGLO):                  -1
SIGDIGITS GRADIENTS (SIGL):                -1
RELATIVE TOLERANCE (TOL):                  -1
ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY (ATOL): -1
EXCLUDE COV FOR FOCE (NOFCOV):              NO
RESUME COV ANALYSIS (RESUME):               NO

TABLES STEP OMITTED:    NO
NO. OF TABLES:           4
SEED NUMBER (SEED):    11456
RANMETHOD:
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MC SAMPLES (ESEED):    300
WRES SQUARE ROOT TYPE:            EIGENVALUE

-- TABLE   1 --
PRINTED:                NO
HEADER:                YES
FILE TO BE FORWARDED:   NO
FORMAT:                S1PE11.4
LFORMAT:
RFORMAT:

USER-CHOSEN ITEMS:
ID TIME MDV IPRE IWRE CWRES

-- TABLE   2 --

4 COLUMNS APPENDED:     NO
PRINTED:                NO
HEADER:                YES
FILE TO BE FORWARDED:   NO
FORMAT:                S1PE11.4
LFORMAT:
RFORMAT:

USER-CHOSEN ITEMS:
ID CL V K HALF ETA1 ETA2

-- TABLE   3 --

4 COLUMNS APPENDED:     NO
PRINTED:                NO
HEADER:                YES
FILE TO BE FORWARDED:   NO
FORMAT:                S1PE11.4
LFORMAT:
RFORMAT:

USER-CHOSEN ITEMS:
ID BWT APGA

-- TABLE   4 --

4 COLUMNS APPENDED:     NO
PRINTED:                NO
HEADER:                YES
FILE TO BE FORWARDED:   NO
FORMAT:                S1PE11.4
LFORMAT:
RFORMAT:

USER-CHOSEN ITEMS:
ID APGA
DOUBLE PRECISION PREDPP VERSION 7.3.0

ONE COMPARTMENT MODEL (ADVAN1)

MAXIMUM NO. OF BASIC PK PARAMETERS:   2

BASIC PK PARAMETERS (AFTER TRANSLATION):
  ELIMINATION RATE (K) IS BASIC PK PARAMETER NO.:  1

TRANSLATOR WILL CONVERT PARAMETERS
CLEARANCE (CL) AND VOLUME (V) TO K (TRANS2)

COMPARTMENT ATTRIBUTES
COMPT. NO.   FUNCTION   INITIAL    ON/OFF      DOSE      DEFAULT    DEFAULT
                        STATUS     ALLOWED    ALLOWED    FOR DOSE   FOR OBS.
   1         CENTRAL      ON         NO         YES        YES        YES
   2         OUTPUT       OFF        YES        NO         NO         NO

ADDITIONAL PK PARAMETERS - ASSIGNMENT OF ROWS IN GG
COMPT. NO.                             INDICES
             SCALE      BIOAVAIL.   ZERO-ORDER  ZERO-ORDER  ABSORB
                        FRACTION    RATE        DURATION    LAG
   1            3           *           *           *           *
   2            *           -           -           -           -
            - PARAMETER IS NOT ALLOWED FOR THIS MODEL
            * PARAMETER IS NOT SUPPLIED BY PK SUBROUTINE;
              WILL DEFAULT TO ONE IF APPLICABLE
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DATA ITEM INDICES USED BY PRED ARE:
  EVENT ID DATA ITEM IS DATA ITEM NO.:      8
  TIME DATA ITEM IS DATA ITEM NO.:          2
  DOSE AMOUNT DATA ITEM IS DATA ITEM NO.:   3


PK SUBROUTINE CALLED WITH EVERY EVENT RECORD.
PK SUBROUTINE NOT CALLED AT NONEVENT (ADDITIONAL OR LAGGED) DOSE TIMES.

ERROR SUBROUTINE CALLED WITH EVERY EVENT RECORD.



#TBLN:      1
#METH: First Order Conditional Estimation with Interaction

ESTIMATION STEP OMITTED:                 NO
ANALYSIS TYPE:                           POPULATION
CONDITIONAL ESTIMATES USED:              YES
CENTERED ETA:                            NO
EPS-ETA INTERACTION:                     YES
LAPLACIAN OBJ. FUNC.:                    NO
NO. OF FUNCT. EVALS. ALLOWED:            9999
NO. OF SIG. FIGURES REQUIRED:            3
INTERMEDIATE PRINTOUT:                   YES
ESTIMATE OUTPUT TO MSF:                  YES
ABORT WITH PRED EXIT CODE 1:             NO
IND. OBJ. FUNC. VALUES SORTED:           NO
NUMERICAL DERIVATIVE
      FILE REQUEST (NUMDER):             NONE
MAP (ETAHAT) ESTIMATION METHOD (OPTMAP): 0
ETA HESSIAN EVALUATION METHOD (ETADER):  0
INITIAL ETA FOR MAP ESTIMATION (MCETA):  0
SIGDIGITS FOR MAP ESTIMATION (SIGLO):    100
GRADIENT SIGDIGITS OF
      FIXED EFFECTS PARAMETERS (SIGL):   100
EXCLUDE TITLE (NOTITLE):                 NO
EXCLUDE COLUMN LABELS (NOLABEL):         NO
NOPRIOR SETTING (NOPRIOR):               OFF
NOCOV SETTING (NOCOV):                   OFF
DERCONT SETTING (DERCONT):               OFF
ABSOLUTE TOLERANCE-ADVAN 9,13 ONLY(ATOL):-100
FINAL ETA RE-EVALUATION (FNLETA):        ON
EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
      IN SHRINKAGE (ETASTYPE):           NO
NON-INFL. ETA CORRECTION (NONINFETA):    OFF
FORMAT FOR ADDITIONAL FILES (FORMAT):    S1PE12.5
PARAMETER ORDER FOR OUTPUTS (ORDER):     TSOL
ADDITIONAL CONVERGENCE TEST (CTYPE=4)?:  NO
EM OR BAYESIAN METHOD USED:                NONE


THE FOLLOWING LABELS ARE EQUIVALENT
PRED=PREDI
RES=RESI
WRES=WRESI
IWRS=IWRESI
IPRD=IPREDI
IRS=IRESI

MONITORING OF SEARCH:



ITERATION NO.:    0    OBJECTIVE VALUE:   816.766780836366        NO. OF FUNC. EVALS.:   6
CUMULATIVE NO. OF FUNC. EVALS.:        6
NPARAMETR:  1.0000E-02  1.0000E+00  1.0000E+00  1.0000E-01  2.0000E-01  1.0000E-01  2.0000E-01
PARAMETER:  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01  1.0000E-01
GRADIENT:   2.4981E+02 -2.8823E+02 -1.2480E+01 -4.3411E+01 -6.8937E+01  1.7895E+02 -6.6195E+01


ITERATION NO.:    5    OBJECTIVE VALUE:   711.060587223237        NO. OF FUNC. EVALS.:   7
CUMULATIVE NO. OF FUNC. EVALS.:       42
NPARAMETR:  5.7830E-03  1.2408E+00  1.0885E+00  1.0361E-01  3.1108E-01  3.0060E-01  3.7372E-01
PARAMETER: -4.4767E-01  3.1572E-01  1.8480E-01  1.3549E-01  3.2087E-01  2.4103E-01 -1.9434E-01
GRADIENT:  -1.3738E+01 -2.8376E+01 -8.2527E-01  8.9304E+00 -3.8046E+00  1.6895E+02  2.6953E+01


ITERATION NO.:   10    OBJECTIVE VALUE:   691.131532110247        NO. OF FUNC. EVALS.:   9
CUMULATIVE NO. OF FUNC. EVALS.:       83
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NPARAMETR:  6.4183E-03  1.4135E+00  1.5510E+00  8.7660E-02  2.5957E-01  1.7184E-01  1.5939E-01
PARAMETER: -3.4342E-01  4.4607E-01  5.3888E-01 -3.1704E-02  2.3036E-01  1.5083E-01 -4.9499E-01
GRADIENT:  -1.2993E+01  1.4579E+01 -5.6555E-01  4.0020E+00  3.8723E+00 -5.4043E+01  1.2411E+01


ITERATION NO.:   15    OBJECTIVE VALUE:   685.704845970756        NO. OF FUNC. EVALS.:   7
CUMULATIVE NO. OF FUNC. EVALS.:      118
NPARAMETR:  6.7077E-03  1.3923E+00  2.1543E+00  7.0192E-02  2.4719E-01  1.9227E-01  1.5709E-01
PARAMETER: -2.9932E-01  4.3097E-01  8.6746E-01 -2.5394E-01  2.0591E-01  1.7295E-01 -1.3958E+00
GRADIENT:   1.1527E+00 -4.9177E+00  2.2834E+00  1.9342E+00 -2.5479E+00  9.6568E+00  7.0105E-01


ITERATION NO.:   20    OBJECTIVE VALUE:   685.540683394105        NO. OF FUNC. EVALS.:   8
CUMULATIVE NO. OF FUNC. EVALS.:      155
NPARAMETR:  6.7377E-03  1.3990E+00  2.2555E+00  6.4447E-02  2.5409E-01  1.9624E-01  1.5547E-01
PARAMETER: -2.9487E-01  4.3574E-01  9.1338E-01 -3.3933E-01  2.1969E-01  1.7410E-01 -1.7236E+00
GRADIENT:   1.5903E-01 -3.0824E-01  1.1965E-01 -7.5686E-02 -3.4194E-02  2.8580E-01  7.3934E-02


ITERATION NO.:   25    OBJECTIVE VALUE:   685.535264086110        NO. OF FUNC. EVALS.:  12
CUMULATIVE NO. OF FUNC. EVALS.:      197
NPARAMETR:  6.7412E-03  1.3992E+00  2.2692E+00  6.4322E-02  2.5388E-01  1.9657E-01  1.5514E-01
PARAMETER: -2.9435E-01  4.3591E-01  9.1945E-01 -3.4127E-01  2.1928E-01  1.7446E-01 -1.8647E+00
GRADIENT:  -4.6081E-01 -3.2044E+00 -4.9072E-02  2.7169E-02 -1.1920E-02  1.7006E-01  9.0601E-04


ITERATION NO.:   28    OBJECTIVE VALUE:   685.525192107303        NO. OF FUNC. EVALS.:   8
CUMULATIVE NO. OF FUNC. EVALS.:      229
NPARAMETR:  6.7834E-03  1.4066E+00  2.2769E+00  6.4007E-02  2.5381E-01  1.9657E-01  1.5507E-01
PARAMETER: -2.8811E-01  4.4120E-01  9.2280E-01 -3.4617E-01  2.1914E-01  1.7450E-01 -1.8865E+00
GRADIENT:   3.6322E-02 -4.0736E-02 -4.1701E-03 -2.5543E-03 -8.1034E-04  1.1083E-01  1.2947E-04

#TERM:

MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED:      229
NO. OF SIG. DIGITS IN FINAL EST.:  3.6

ETABAR IS THE ARITHMETIC MEAN OF THE ETA-ESTIMATES,
AND THE P-VALUE IS GIVEN FOR THE NULL HYPOTHESIS THAT THE TRUE MEAN IS 0.

ETABAR:        -4.6545E-03 -3.9034E-03
SE:             6.4054E-02  5.0241E-02
N:                      59          59

P VAL.:         9.4207E-01  9.3807E-01

ETAshrink(%):   1.5019E+00  1.1578E+00
EBVshrink(%):   2.2369E+00  1.8965E+00
EPSshrink(%):   2.1210E+01

#TERE:
Elapsed estimation time in seconds:     1.06
Elapsed covariance time in seconds:     0.36
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********************************************************************************************************************
********************                                                                        ********************
********************              FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION       ********************
#OBJT:**************                      MINIMUM VALUE OF OBJECTIVE FUNCTION               ********************
********************                                                                        ********************
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#OBJV:**********   685.525   **********

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**********   **********
**********   FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION   **********
**********   FINAL PARAMETER ESTIMATE   **********
**********   **********
****

THETA - VECTOR OF FIXED EFFECTS PARAMETERS   *********

TH 1	TH 2	TH 3	TH 4
6.78E-03	1.41E+00	2.28E+00	6.40E-02

OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS ********

	ETA1	ETA2
ETA1	2.54E-01	
ETA2	1.97E-01	1.55E-01

SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS ****

	EPS1
EPS1	1.00E+00

OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS *******

	ETA1	ETA2
ETA1	5.04E-01	
ETA2	9.91E-01	3.94E-01

SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS ***

	EPS1
EPS1	1.00E+00

****
**********   **********
**********   FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION   **********
**********   STANDARD ERROR OF ESTIMATE   **********
**********   **********
****

THETA - VECTOR OF FIXED EFFECTS PARAMETERS   *********

TH 1	TH 2	TH 3	TH 4

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        5.17E-04  7.48E-02  7.42E-01  3.15E-02


OMEGA - COV MATRIX FOR RANDOM EFFECTS - ETAS  ********

           ETA1      ETA2

ETA1    7.61E-02

ETA2    5.06E-02  3.98E-02


SIGMA - COV MATRIX FOR RANDOM EFFECTS - EPSILONS  ****

           EPS1

EPS1   .........



OMEGA - CORR MATRIX FOR RANDOM EFFECTS - ETAS  *******

           ETA1      ETA2

ETA1    7.55E-02

ETA2    4.97E-02  5.05E-02


SIGMA - CORR MATRIX FOR RANDOM EFFECTS - EPSILONS  ***

           EPS1

EPS1   .........

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********************                                                                        ********************
********************               FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION       ********************
********************                         COVARIANCE MATRIX OF ESTIMATE                  ********************
********************                                                                        ********************
************************************************************************************************************************


           TH 1      TH 2      TH 3      TH 4      OM11      OM12      OM22      SG11

TH 1    2.67E-07

TH 2    2.95E-05  5.59E-03

TH 3   -7.23E-05 -2.50E-03  5.51E-01

TH 4    2.16E-06 -1.45E-04 -2.05E-02  9.90E-04

OM11    5.98E-06  2.83E-03  9.96E-03 -5.17E-04  5.79E-03

OM12    9.36E-06  2.24E-03  4.25E-03 -2.24E-04  3.63E-03  2.56E-03

OM22    1.18E-05  1.61E-03 -7.99E-03  2.85E-04  1.93E-03  1.66E-03  1.58E-03

SG11   ......... ......... ......... ......... ......... ......... ......... .........

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********************                                                                        ********************
********************               FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION       ********************
********************                         CORRELATION MATRIX OF ESTIMATE                 ********************
********************                                                                        ********************
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	TH 1	TH 2	TH 3	TH 4	OM11	OM12	OM22	SG11
TH 1	5.17E−04							
TH 2	7.62E−01	7.48E−02						
TH 3	−1.88E−01	−4.51E−02	7.42E−01					
TH 4	1.33E−01	−6.18E−02	−8.77E−01	3.15E−02				
OM11	1.52E−01	4.97E−01	1.76E−01	−2.16E−01	7.61E−02			
OM12	3.58E−01	5.93E−01	1.13E−01	−1.41E−01	9.42E−01	5.06E−02		
OM22	5.73E−01	5.41E−01	−2.71E−01	2.27E−01	6.38E−01	8.25E−01	3.98E−02	
SG11	.....	.....	.....	.....	.....	.....	.....	.....

****
****
********** FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION **********
********** INVERSE COVARIANCE MATRIX OF ESTIMATE **********
****
****

	TH 1	TH 2	TH 3	TH 4	OM11	OM12	OM22	SG11
TH 1	1.90E+07							
TH 2	−1.04E+05	9.04E+02						
TH 3	−3.18E+03	3.80E+01	1.20E+01					
TH 4	−2.18E+04	4.20E+02	1.84E+02	4.80E+03				
OM11	3.79E+04	2.28E+02	1.06E+02	6.69E+02	5.28E+03			
OM12	1.02E+05	−1.77E+03	−3.13E+02	−1.45E+03	−1.16E+04	2.94E+04		
OM22	−2.01E+05	1.55E+03	2.12E+02	5.04E+02	5.61E+03	−1.70E+04	1.26E+04	
SG11	.....	.....	.....	.....	.....	.....	.....	.....

#CPUT: Total CPU Time in Seconds, 1.406