```
NONLINEAR MIXED EFFECTS MODEL PROGRAM (NONMEM) VERSION 7.4.1
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
GRADIENT METHOD USED:     NOSLOW
SIGDIGITS ETAHAT (SIGLO):                  -1
SIGDIGITS GRADIENTS (SIGL):                -1
EXCLUDE COV FOR FOCE (NOFCOV):              NO
TURN OFF Cholesky Transposition of R Matrix (CHOLROFF): NO
KNUTHSUMOFF:                                -1
RESUME COV ANALYSIS (RESUME):               NO
SIR SAMPLE SIZE (SIRSAMPLE):              -1
NON-LINEARLY TRANSFORM THETAS DURING COV (THBND): 1
PRECONDTIONING CYCLES (PRECOND):        0
PRECONDTIONING TYPES (PRECONDS):        TOS
```

```
FORCED PRECONDTIONING CYCLES (PFCOND):0
PRECONDTIONING TYPE (PRETYPE):        0
FORCED POS. DEFINITE SETTING: (FPOSDEF):0

TABLES STEP OMITTED:    NO
NO. OF TABLES:           4
SEED NUMBER (SEED):    11456
RANMETHOD:             3U
MC SAMPLES (ESAMPLE):    300
WRES SQUARE ROOT TYPE (WRESCHOL): EIGENVALUE

-- TABLE   1 --

RECORDS ONLY:    ALL

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

USER-CHOSEN ITEMS:
ID TIME MDV IPRE IWRE CWRES

-- TABLE   2 --

RECORDS ONLY:    ALL

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

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

-- TABLE   3 --

RECORDS ONLY:    ALL

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

USER-CHOSEN ITEMS:
ID BWT APGA

-- TABLE   4 --

RECORDS ONLY:    ALL

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

USER-CHOSEN ITEMS:
ID APGA
DOUBLE PRECISION PREDPP VERSION 7.4.1

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

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
NUMBER OF SADDLE POINT RESET ITERATIONS:      0
GRADIENT METHOD USED:               NOSLOW
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
NOPRIOR SETTING (NOPRIOR):                 OFF
NOCOV SETTING (NOCOV):                     OFF
DERCONT SETTING (DERCONT):                 OFF
FINAL ETA RE-EVALUATION (FNLETA):          ON
EXCLUDE NON-INFLUENTIAL (NON-INFL.) ETAS
      IN SHRINKAGE (ETASTYPE):             NO
NON-INFL. ETA CORRECTION (NONINFETA):      OFF
RAW OUTPUT FILE (FILE): 2005.ext
EXCLUDE TITLE (NOTITLE):                   NO
EXCLUDE COLUMN LABELS (NOLABEL):           NO
FORMAT FOR ADDITIONAL FILES (FORMAT):      S1PE12.5
PARAMETER ORDER FOR OUTPUTS (ORDER):       TSOL
WISHART PRIOR DF INTERPRETATION (WISHTYPE):0
KNUTHSUMOFF:                               0
INCLUDE LNTWOPI:                           NO
INCLUDE CONSTANT TERM TO PRIOR (PRIORC):   NO
INCLUDE CONSTANT TERM TO OMEGA (ETA) (OLNTWOPI):NO
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:   711.060586376867        NO. OF FUNC. EVALS.:  36
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:   691.131417646534        NO. OF FUNC. EVALS.:  41
CUMULATIVE NO. OF FUNC. EVALS.:       83
NPARAMETR:  6.4184E-03  1.4135E+00  1.5510E+00  8.7660E-02  2.5957E-01  1.7183E-01  1.5939E-01
PARAMETER: -3.4342E-01  4.4607E-01  5.3889E-01 -3.1705E-02  2.3036E-01  1.5083E-01 -4.9500E-01
GRADIENT:  -1.2992E+01  1.4579E+01 -5.6559E-01  4.0019E+00  3.8721E+00 -5.4048E+01  1.2411E+01


ITERATION NO.:   15    OBJECTIVE VALUE:   685.704738210397        NO. OF FUNC. EVALS.:  35
CUMULATIVE NO. OF FUNC. EVALS.:      118
NPARAMETR:  6.7077E-03  1.3923E+00  2.1541E+00  7.0195E-02  2.4720E-01  1.9228E-01  1.5709E-01
PARAMETER: -2.9933E-01  4.3097E-01  8.6738E-01 -2.5390E-01  2.0594E-01  1.7295E-01 -1.3957E+00
GRADIENT:   1.1456E+00 -4.9066E+00  2.2781E+00  1.9320E+00 -2.5448E+00  9.6489E+00  7.0085E-01


ITERATION NO.:   20    OBJECTIVE VALUE:   685.540731915364        NO. OF FUNC. EVALS.:  37
CUMULATIVE NO. OF FUNC. EVALS.:      155
NPARAMETR:  6.7378E-03  1.3990E+00  2.2549E+00  6.4481E-02  2.5411E-01  1.9624E-01  1.5548E-01
PARAMETER: -2.9485E-01  4.3576E-01  9.1311E-01 -3.3880E-01  2.1972E-01  1.7410E-01 -1.7213E+00
GRADIENT:   1.6232E-01 -2.9880E-01  1.3122E-01 -6.5885E-02 -3.3396E-02  3.0320E-01  7.5507E-02


ITERATION NO.:   25    OBJECTIVE VALUE:   685.535279891691        NO. OF FUNC. EVALS.:  38
CUMULATIVE NO. OF FUNC. EVALS.:      193
NPARAMETR:  6.7408E-03  1.3992E+00  2.2728E+00  6.4135E-02  2.5384E-01  1.9655E-01  1.5510E-01
PARAMETER: -2.9441E-01  4.3588E-01  9.2101E-01 -3.4418E-01  2.1920E-01  1.7447E-01 -1.8714E+00
GRADIENT:   5.0171E-03 -2.9098E-02  9.3757E-02  1.0926E-02 -8.4871E-03  9.9333E-02  1.7816E-03


ITERATION NO.:   29    OBJECTIVE VALUE:   685.525192050602        NO. OF FUNC. EVALS.:  52
CUMULATIVE NO. OF FUNC. EVALS.:      245
NPARAMETR:  6.7834E-03  1.4066E+00  2.2768E+00  6.4010E-02  2.5381E-01  1.9657E-01  1.5507E-01
PARAMETER: -2.8811E-01  4.4120E-01  9.2279E-01 -3.4613E-01  2.1914E-01  1.7449E-01 -1.8864E+00
GRADIENT:   3.6549E-02 -4.1369E-02 -2.6860E-03 -1.4247E-03 -9.3274E-04  1.1162E-01  1.7977E-04

#TERM:

MINIMIZATION SUCCESSFUL
NO. OF FUNCTION EVALUATIONS USED:      245
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:        -4.6538E-03 -3.9029E-03
SE:             6.4054E-02  5.0241E-02
N:                      59          59

P VAL.:         9.4208E-01  9.3808E-01

ETASHRINKSD(%)  1.5020E+00  1.1579E+00
ETASHRINKVR(%)  2.9815E+00  2.3023E+00
EBVSHRINKSD(%)  2.2370E+00  1.8965E+00
EBVSHRINKVR(%)  4.4239E+00  3.7570E+00
```

EPSSHRINKSD(%) 2.1211E+01
EPSSHRINKVR(%) 3.7922E+01

TOTAL DATA POINTS NORMALLY DISTRIBUTED (N):   155
N*LOG(2PI) CONSTANT TO OBJECTIVE FUNCTION: 284.87094529344853
OBJECTIVE FUNCTION VALUE WITHOUT CONSTANT: 685.52519205060185
OBJECTIVE FUNCTION VALUE WITH CONSTANT: 970.39613734405043
REPORTED OBJECTIVE FUNCTION DOES NOT CONTAIN CONSTANT

TOTAL EFFECTIVE ETAS (NIND*NETA):   118

#TERE:
Elapsed estimation time in seconds: 3.16
Elapsed covariance time in seconds: 0.63
Elapsed postprocess time in seconds: 0.02

****
********************   ********************
********************   FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION   ********************
#OBJT:**********   MINIMUM VALUE OF OBJECTIVE FUNCTION   ********************
********************   ********************
****

#OBJV:***   685.525   **

****
********************   ********************
********************   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
5.17E-04	7.47E-02	7.39E-01	3.13E-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	4.96E-02	5.05E-02

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

```
        EPS1

EPS1    .........
```

```
********************************************************************************************************************
********************                                                                            ********************
********************               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     2.94E-05  5.59E-03

TH 3    -7.35E-05 -2.70E-03  5.46E-01

TH 4     2.22E-06 -1.35E-04 -2.02E-02  9.77E-04

OM11     5.96E-06  2.82E-03  9.89E-03 -5.14E-04  5.79E-03

OM12     9.34E-06  2.24E-03  4.19E-03 -2.21E-04  3.63E-03  2.56E-03

OM22     1.18E-05  1.61E-03 -7.97E-03  2.84E-04  1.93E-03  1.66E-03  1.58E-03

SG11    ......... ......... ......... ......... ......... ......... ......... .........
```

```
********************************************************************************************************************
********************                                                                            ********************
********************               FIRST ORDER CONDITIONAL ESTIMATION WITH INTERACTION           ********************
********************                          CORRELATION MATRIX OF ESTIMATE                    ********************
********************                                                                            ********************
********************************************************************************************************************
```

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

TH 1     5.17E-04

TH 2     7.62E-01  7.47E-02

TH 3    -1.92E-01 -4.89E-02  7.39E-01

TH 4     1.38E-01 -5.76E-02 -8.76E-01  3.13E-02

OM11     1.51E-01  4.97E-01  1.76E-01 -2.16E-01  7.61E-02

OM12     3.57E-01  5.93E-01  1.12E-01 -1.40E-01  9.42E-01  5.06E-02

OM22     5.74E-01  5.42E-01 -2.71E-01  2.28E-01  6.38E-01  8.26E-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    -3.19E+03  3.80E+01  1.20E+01

TH 4    -2.21E+04  4.19E+02  1.84E+02  4.83E+03

OM11     3.78E+04  2.28E+02  1.06E+02  6.71E+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  5.00E+02  5.61E+03 −1.70E+04  1.26E+04

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

Elapsed finaloutput time in seconds:     1.06
#CPUT: Total CPU Time in Seconds,        2.387
```