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Clinical Trial Simulation

Using NONMEM

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NONMEM Example

```
$PROB THEOPHYLLINE PHARMACODYNAMICS $PRED
$DATA theopd.dat IGNORE #           S0=POP_S0*EXP (PPV_S0)
$INPUT ID TIME THEO AGE WT GEND RACE EMAX=POP_EMAX*EXP (PPV_EMAX)
DIAG DV                               C50=POP_C50*EXP (PPV_C50)
$SIM (20000625 NORMAL NEW)           EFFECT=S0 + EMAX*THEO/(THEO+C50)
SUBPROBLEMS=100                       Y = EFFECT + RUV_SD
$ESTIM PRINT=0 ; suppress output      IF (ICALL.EQ.4) THEN
$THETA (0,150.,) ; POP_S0              DOWHILE (Y.LT.0)
$THETA (0,200.,) ; POP_EMAX            CALL SIMEPS (EPS)
$THETA (.001,10,) ; POP_C50            Y=EFFECT + RUV_SD
$OMEGA BLOCK(3)                        ENDDO
0.25 ; PPV_S0                           ENDIF
0.01 0.25 ; PPV_EMAX
0.01 0.01 0.25 ; PPV_C50
$$SIGMA 100 ; RUV_SD
```

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Simulating Continuous Covariates

```
IF (ICALL.EQ.4) THEN ; Simulation
; Simulate Weight Distribution (for male)
WTMALE=WTSTD*EXP (PPV_WT)
LO=40 ; kg
HI=200 ; kg
DOWHILE (WTMALE.LT.LO .OR. WTMALE.GT.HI)
CALL SIMETA (ETA)
WTMALE = WTSTD*EXP (PPV_WT)
ENDDO
etc
```

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Simulating Categorical Covariates

```
$SIM (20000625 NORMAL NEW) (20010112 UNIFORM)
SUBPROBLEMS=100

$PK ; Simulate Sex Distribution
FEMALE=0.5 ; proportion of females
CALL RANDOM(2,R) ; 2nd random number generator
IF (R.GT.FEMALE) THEN
  SEX=1 ;male
  WT=WTMALE ; previously simulated male WT
ELSE
  SEX=0 ;female
  WT=0.85*WTMALE ; weight for female
ENDIF
etc
```

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Truncating Parameters

```
IF (ICALL.EQ.4) THEN ; simulation within 99.9% of full Normal
  TRUNC=3.27 ; Z 2tailed alpha=0.01 i.e. include 99.9%
  GRPS0=POP_S0 ; include covariate effects here if needed
  S0=GRPE0*EXP(PFV_E0)
  LNMU=LOG(GRP_E0)
  DLTA=TRUNC*0.717 ; Must be TRUNC*SQRT(PFV_E0)!
  LO=EXP(LNMU-DLTA)
  HI=EXP(LNMU+DLTA)
  DOWHILE (S0.LT.LO .OR. S0.GT.HI)
  CALL SIMETA(ETA)
  S0=GRPS0*EXP(PFV_S0)
ENDDO
etc
```

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