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Clinical Trial Simulation

Using NONMEM

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NONMEM Example

```
$PROB THEOPHYLLINE PHARMACODYNAMICS
$DATA theopd.dat IGNORE #
$INPUT ID TIME THEO AGE WT GEND RACE
DIAG DV
$SIM (20000625 NORMAL NEW)
SUBPROBLEMS=100
$ESTIM PRINT=0 ; suppress output
$THETA (0,150.,)  ; POP_S0
$THETA (0,200.,)  ; POP_EMAX
$THETA (.001,10,) ; POP_C50
$OMEGA BLOCK(3)
0.25  ; PPV_S0
0.01 0.25  ; PPV_EMAX
0.01 0.01 0.25  ; PPV_C50
$SIGMA 100 ; RUV_SD
```

```
$PRED
 S0=POP_S0*EXP(PPV_S0)
 EMAX=POP_EMAX*EXP(PPV_EMAX)
 C50=POP_C50*EXP(PPV_C50)
 EFFECT=S0 + EMAX*THEO/(THEO+C50)
 Y =  EFFECT + RUV_SD
 IF (ICALL.EQ.4) THEN
     DOWHILE (Y.LT.0)
         CALL SIMEPS(EPS)
         Y=EFFECT + RUV_SD
     ENDDO
 ENDIF
```


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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(PPV_E0)
      LNMU=LOG(GRP_E0)
      DLTA=TRUNC*0.717 ; Must be TRUNC*SQRT(PPV_E0)!
      LO=EXP(LNMU-DLTA)
      HI=EXP(LNMU+DLTA)
      DOWHILE (S0.LT.LO .OR. S0.GT.HI)
         CALL SIMETA(ETA)
         S0=GRPS0*EXP(PPV_S0)
      ENDDO
      etc
```


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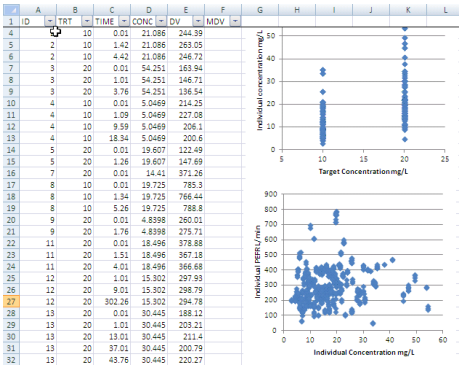
Hands-On

- Original data from RCCT of theophylline
- Use original data to obtain model parameters
- Simulate a Randomized Concentration Controlled Trial using NONMEM
- Evaluate model analysis scenarios
  - Placebo vs Target (10 or 20 mg/L)
  - Placebo vs Actual Concentration

Holford N, Black P, Couch R, Kennedy J, Briant R. Theophylline target concentration in severe airways obstruction - 10 or 20 mg/L? A randomised concentration-controlled trial. Clin Pharmacokinet 1993; 25: 495-505.

Slide 7	# Fit Original Data THETA: POP_S0 POP_EMAX POP_C50 RUV_SD ETA: PPV_S0 PPV_EMAX PPV_C50 ERR: EPS1 theopd_org.lst 5800.202 FOCE eval=308 sig=3.3 sub=153 obs=574 MOD(N THETA = 143 180 7.6 79.7 ETASD = 0.430116 0.43359 1.32665 ETAR12 = 0.082 ETAR23 = 0.960 -0.121 ETAPval = 0.0029592 0.8703 0.0010115 ETAshr% = 57.948 22.373 61.74 EPSshr% = 9.7933 EPSSD = 1 MINIMIZATION SUCCESSFUL HOWEVER, PROBLEMS OCCURRED WITH THE MINIMIZATION. REGARD THE RESULTS OF THE ESTIMATION STEP CAREFULLY, AND ACCEPT THEM ONLY AFTER CHECKING THAT THE COVARIANCE STEP PRODUCES REASONABLE OUTPUT. Ttot 0:3.86 Test 0:2.36 Tcov 0:0 Ttcl 0:1.5 C:\Docs\Mtg\12\PAGANZ Monash\PAWS\Intermediate\CTS\NM72> 	
Slide 8	# Simulate Data $MDV DATA ITEM. CREATING MUMODEL ROUTINE... Completed call to gfcompile.bat NONMEM theopd_sim... License Registered to: PKPDRX Limited Expiration Date: 14 NOV 2012 Current Date: 9 SEP 2012 Days until program expires : 65 PROBLEM NO.: 1 SUBPROBLEM NO.: 1 THETA: F_10 POP_S0 POP_EMAX POP_C50 RUV_SD ETA: PPV_CONC PPV_S0 PPV_EMAX PPV_C50 ERR: EPS1 theopd_sim.lst ******* NNNN eval=0 sig=0 sub=153 obs=574 MOD(NONMEM)7.2.0 ESTIMATION OMITTED Ttot 0:0 Test 0:0 Tcov 0:0 Ttcl 0:0 C:\Docs\Mtg\12\PAGANZ Monash\PAWS\Intermediate\CTS\NM72> 	
Slide 9	# Examine Simulation In Excel  	

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No Effect Estimation

```
$PROB theophylline concentration controlled trial
$DATA ..\theopd_sim_trunc.reg\theopd_sim_trunc.fit
IGNORE @
$INPUT ID TRT TIME CONC DV MDV

$ESTIM METHOD=COND
NSIG=3 SIGL=9

$THETA
(0,150.,)      ; POP_S0 L/min
(0,10,) ; RUV_SD L/min

$OMEGA BLOCK(1)
0.25    ; PPV_S0                $PRED
                                S0=POP_S0*EXP(PPV_S0)
$SIGMA 1 FIX   ; EPS1           Y = S0 + RUV_SD*EPS1
```


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Treatment Target Estimation

```
$PROB theophylline concentration controlled trial
$DATA ..\theopd_sim_trunc.reg\theopd_sim_trunc.fit
IGNORE @
$INPUT ID TRT TIME CONC DV MDV

$ESTIM METHOD=COND
NSIG=3 SIGL=9

$THETA
(0,150.,)      ; POP_S0 L/min
20      ; POP_EFF10 L/min
20      ; POP_EFF20 L/min
                                $PRED
(0,10,) ; RUV_SD                S0=POP_S0*EXP(PPV_S0)
                                IF (TRT.EQ.10) THEN
$OMEGA BLOCK(2)                    EFFECT=POP_EFF10*(1+PPV_EFFECT)
0.25    ; PPV_S0                ELSE
0.01 0.25      ; PPV_EFFECT        EFFECT=POP_EFF20*(1+PPV_EFFECT)
                                ENDIF
$SIGMA 1 FIX   ; EPS1           Y = S0 + EFFECT + RUV_SD*EPS1
```


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Actual Concentration Estimation

```
$PROB theophylline concentration controlled trial
$DATA ..\theopd_sim_trunc.reg\theopd_sim_trunc.fit
IGNORE @
$INPUT ID TRT TIME CONC DV MDV

$ESTIM METHOD=COND
NSIG=3 SIGL=9

$THETA
(0,150.,)      ; POP_S0 L/min
200.    ; POP_EMAX L/min
(.1,10,); POP_C50 mg/L

(0,10,) ; RUV_SD L/min          $PRED

$OMEGA BLOCK(3)                 S0=POP_S0*EXP(PPV_S0)
0.25 ; PPV_S0                   EMAX=POP_EMAX*(1+PPV_EMAX)
0.01 0.25 ; PPV_EMAX            C50=POP_C50*EXP(PPV_C50)
0.01 0.01 0.25 ; PPV_C50
                                EFFECT= S0 + EMAX*CONC/(CONC+C50)
$SIGMA 1 FIX   ; EPS1           Y = EFFECT + RUV_SD*EPS1
```

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Simulate and Estimate

```
rem To create and delete simulated data: set ctsthisgotdata=
rem To create and keep simulated data:   set ctsthisgotdata=n
rem To skip creation and keep sim data:  set ctsthisgotdata=y
rem Non-default simulated data dir:      set ctsdata=non_default_dir
rem create and keep simulated data, estimate with placebo model


set ctsthisgotdata=n
call nmgosim theopd_sim_trunc trial_placebo_est 1 10

rem use simulated data, estimate with treatment model
set ctsthisgotdata=y
call nmgosim theopd_sim_trunc trial_trt_est 1 10

rem use simulated data, estimate with concentration model
set ctsthisgotdata=y
call nmgosim theopd_sim_trunc trial_conc_est 1 10
```


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Power

Obj	Obj	DeltaConc	df	P	Significant
4172.766	4165.529	7.237	4	0.123881474	0
4095.863	4086.683	9.18	4	0.056754478	0
4060.57	4051.011	9.559	4	0.048548944	1
4083.553	4077.46	6.093	4	0.192309795	0
4073.254	4060.229	13.025	4	0.011154283	1
4136.384	4134.839	1.545	4	0.8186415	0
4088.738	4057.031	31.707	4	2.19585E-06	1
4152.024	4137.328	14.696	4	0.0053751	1
4137.879	4124.76	13.119	4	0.010708741	1
4096.63	4077.816	18.814	4	0.000854904	1

Treatment Target

alpha	power
0.05	60%

Obj	Obj	DeltaConc	df	P	Significant
4172.766	4157.233	15.533	7	0.02974275	1
4095.863	4079.548	16.315	7	0.022389236	1
4060.57	4042.434	18.136	7	0.011371235	1
4083.553	4056.732	26.821	7	0.000358927	1
4073.254	4054.526	18.728	7	0.009083485	1
4136.384	4120.128	16.256	7	0.022877696	1
4088.738	4067.576	21.162	7	0.003537637	1
4152.024	4131.046	20.978	7	0.003802848	1
4137.879	4119.766	18.113	7	0.011470439	1
4096.63	4065.427	31.203	7	5.70359E-05	1

Actual Concentration

alpha	power
0.05	100%

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Simulation Tools

- NONMEM
  - Easy to simulate from estimation model
- Wings for NONMEM
  - Support for NONMEM estimation to test scenarios
- Excel
  - Graphical check of simulation
  - Power Calculation