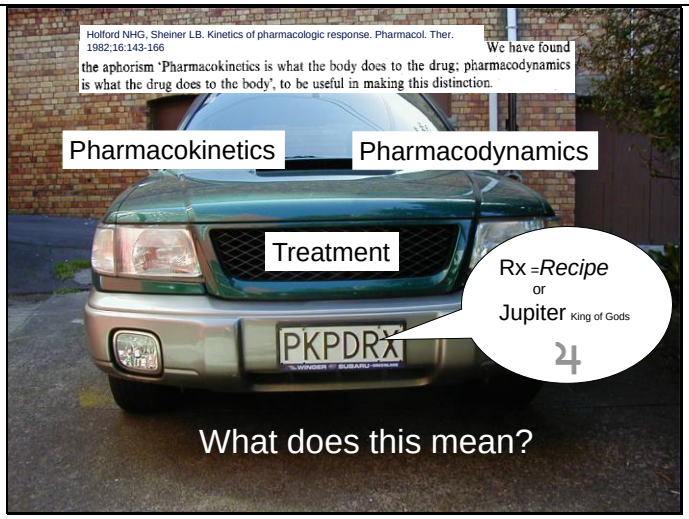
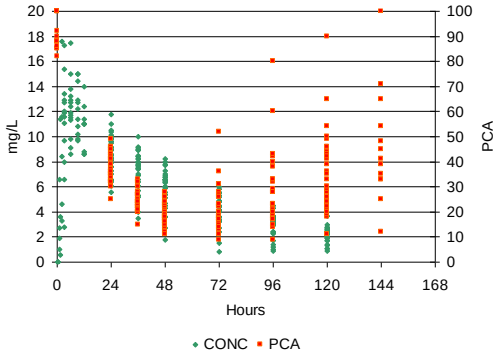
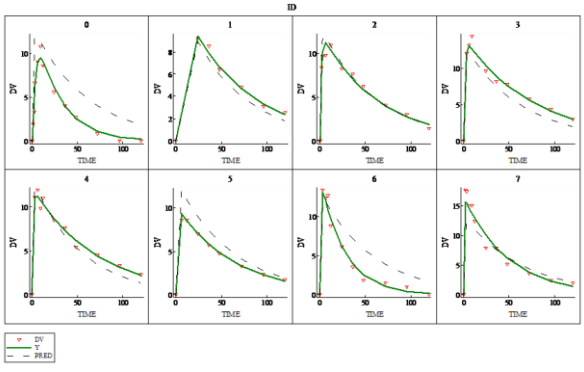
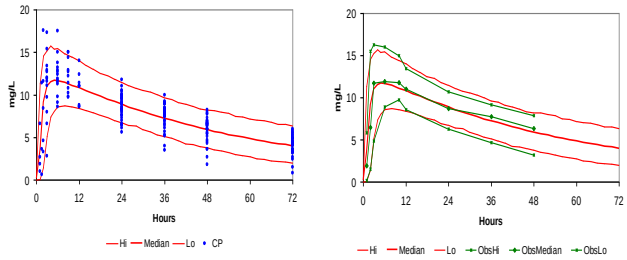
Slide 1	# PKPD ## Workshop Nick Holford Dept Pharmacology & Clinical Pharmacology University of Auckland, New Zealand 	
Slide 2		PK = Pharmacokinetics: What the body does to the drug PD=Pharmacodynamics: What the drug does to the body Rx=Treatment: What the prescribed and patient need to know.

Slide 3	## Warfarin Data
	
	- PKPD Studies in Healthy Subjects
	  – 1.5 mg/kg single oral dose
	  – Total racemic warfarin plasma concentration
	  – Prothrombin complex activity (PCA)
	- 32 subjects, 250 concentrations, 232 PCA
	
	- O'Reilly RA, Aggeler PM, Leong LS. Studies of the coumarin anticoagulant drugs: The pharmacodynamics of warfarin in man. Journal of Clinical Investigation 1963;42(10):1542-1551
	- O'Reilly RA, Aggeler PM. Studies on coumarin anticoagulant drugs Initiation of warfarin therapy without a loading dose. Circulation 1968;38:169-177
	
		A classical clinical pharmacology study from 40 years ago.
		Prothrombin complex activity is inversely proportional to the International Normalized Ratio (INR)

Slide 4	**Warfarin Observations**  	Two features to notice about the time course of warfarin concentration and effect on PCA: • Peak concentration is about 6 h while greatest effect is at 72 h • Most marked between subject variability in PCA occurs when PK variability is least

Slide 5	**PK Model**
	`$PROB Warfarin PKPD`
	`$INPUT ID time wt age sex amt dvid dv mdv`
	`$DATA warfarin_conc_pca.csv`
	`IGNORE (DVID.EQ.2) ; Don't include PCA`
	`$EST METHOD=COND INTER`
	`MAX=9990 NSIG=3 SIGL=9 PRINT=20 NOABORT`
	`$COV`
	`$THETA`
	`(0.01,0.134,1) ; POP_CL L/h/70kg`
	`(0.01,8.11,20) ; POP_V L/70kg`
	`(0.01,0.523,24) ; POP_TABS h`
	`(0.01,0.823,24) ; POP_LAG h`
	`$OMEGA`
	`0.0713 ; PPV_CL`
	`0.0181 ; PPV_V`
	`0.696 ; PPV_TABS`
	`0.156 ; PPV_LAG`
	`$SIGMA`
	`0.00752 ; RUV_CV`
	`0.0661 ; RUV_SD mg/L`
	`$SUBR ADVAN2 TRAN2`
	`$PK`
	`IF (NEWIND.LE.1) LN2=LOG(2)`
	`FSZV=WT/70`
	`FSZCL=FSZV**0.75`
	`CL=FSZCL*POP_CL*EXP(PPV_CL)`
	`V=FSZV*POP_V*EXP(PPV_V)`
	`TABS=POP_TABS*EXP(PPV_TABS)`
	`TLAG=POP_LAG*EXP(PPV_LAG)`
	`KA=LN2/TABS`
	`ALAG1=TLAG`
	`S2=V`
	`$ERROR`
	`CP=F`
	`Y=CP*(1+RUV_CV) + RUV_SD`
	
		One compartment model with first-order absorption and lag time.
		Note the use of IGNORE on the $DATA record so that only concentration observations are used in the fit (DVID=2 means PCA observation record).

Slide 6	**Warfarin First-Order Input (KA1L)**  	Individual "post hoc" predictions of concentration fit the time course well and should be adequate for driving the pharmacodynamic model.

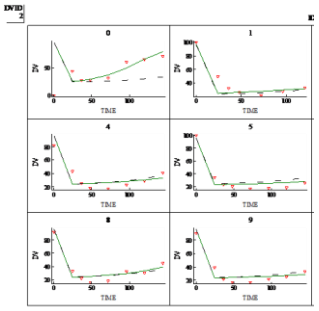
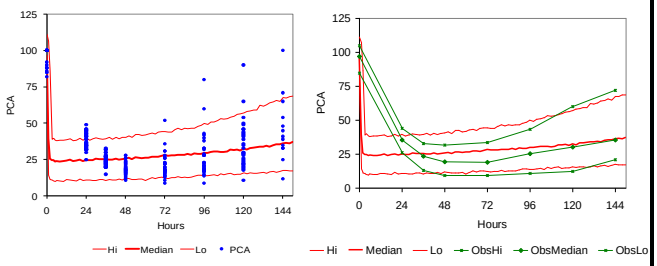
Slide 7	**Warfarin KA1L Predictive Check**  	The visual predictive check reveals that the model overestimates the early variability in concentration.
Slide 8	**Immediate Effect Model** • Two Basic Approaches – PREDPP • ADVAN2 • ADVAN6 Differential Equations – $PRED • Write model for CP 	An immediate effect model uses central compartment concentrations to predict the drug effect. Concentrations can be predicted using $PRED or one of the PREDPP library ADVAN subroutines. Using ADVAN subroutines is usually easier to code but the model is not so clear.

Slide 9	**Central Compartment Using ADVAN2**
	`$SUB ADVAN2 TRANS2`
	`$PK`
	`; Define LN2 for efficiency`
	`IF (NEWIND.EQ.0) THEN`
	`LN2=LOG(2)`
	`ENDIF`
	`; Define parameters`
	`KA=LN2/TABS`
	`ALAG1=TLAG`
	`S2=V`
	`$ERROR`
	`CP=A(2)/V ; or CP=F`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUV_CV) + RUV_SD`
	`ENDIF`
	`CE=CP`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUV_FX`
	`ENDIF`
	
		TABS is the half-life of absorption. The absorption rate is parameterised in terms of TABS but because ADVAN2 requires a value for KA it must be calculated from TABS in the code. The NEWIND variable is a built in feature of NONMEM. When it is <= 1 it means this is the first record for this individual. The variable LN2 is calculated from LOG(2) just once for efficiency.
		Note how the DVID data item is used to distinguish predictions of concentration (DVID=1) from predictions of PCA (DVID=2).

Slide 10	**Data for Joint PKPD Model** #ID time wt age sex amt dvid dv mdv 1 0 66.7 50 1 100 0 . 1 1 0 66.7 50 1 . 2 . 1 1 0.5 66.7 50 1 . 1 0 0 1 1 66.7 50 1 . 1 1.9 0 1 2 66.7 50 1 . 1 3.3 0 1 3 66.7 50 1 . 1 6.6 0 1 6 66.7 50 1 . 1 9.1 0 1 9 66.7 50 1 . 1 10.8 0 1 12 66.7 50 1 . 1 8.6 0 1 24 66.7 50 1 . 1 5.6 0 1 24 66.7 50 1 . 2 44 0 1 36 66.7 50 1 . 1 4 0 1 36 66.7 50 1 . 2 27 0 1 48 66.7 50 1 . 1 2.7 0 1 48 66.7 50 1 . 2 28 0 1 72 66.7 50 1 . 1 0.8 0 1 72 66.7 50 1 . 2 31 0 1 96 66.7 50 1 . 1 . 1 1 96 66.7 50 1 . 2 60 0 1 120 66.7 50 1 . 1 . 1 1 120 66.7 50 1 . 2 65 0 1 144 66.7 50 1 . 2 71 0 	NONMEM requires that all observations are in a single DV column. In order to distinguish concentrations from effects (PCA) the DVID data item is used to identify the kind of DV. A DVID of 0 is used to indicate a dose record, 1 for a concentration record and 2 for a PCA record. Note that MDV is used to indicate if there are missing observations e.g. this subject does not have a PCA observation at TIME=0.

Slide 11	**Central Compartment Using ADVAN6**
	
	`$SUBR ADVAN6 TOL=9`
	`$MODEL`
	`  COMP (GUT)`
	`  COMP (CENTRAL)`
	`$PK`
	`; Define LN2`
	`  IF (NEWIND.LE.1) THEN`
	`  LN2=LOG(2)`
	`  ENDIF`
	`; Define parameters`
	`  KA=LN2/TABS`
	`  ALAG1=TLAG`
	`  S2=V`
	
	`$DES`
	`  GUT=A(1)`
	`  DCP=A(2)/V`
	
	`  RATEIN=KA*GUT`
	`  DADT(1)= -RATEIN`
	`  DADT(2)= RATEIN - DCP*CL`
	
	`$ERROR`
	
	`  CP=A(2)/V`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`  CE=CP`
	`  PCA=E0 + EMAX*CE/(C50+CE)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
		Note the variables defined in $DES cannot have the same name as variables in other blocks e.g. you cannot define CP=A(2)/V in $DES and also in $ERROR. In this example the variable name DCP is used in $DES and the variable name CP is used in $ERROR.
		
		http://clinpharmacol.fmhs.auckland.ac.nz/docs/warfarin.csv

Slide 12	**Central Compartment Using $PRED**
	
	`$PRED`
	`; Get DOSE from AMT`
	`  IF (NEWIND.LE.1) THEN`
	`  LN2=LOG(2)`
	`  DOSE=0`
	`  ENDIF`
	`  IF (AMT.GT.0) DOSE=AMT`
	
	`; Define parameters`
	`  KA=LN2/TABS`
	`  KE=CL/V`
	
	`; Adjust time for lagtime`
	`  IF (TIME.LE.TLAG) THEN`
	`  TAD=0`
	`  ELSE`
	`  TAD=TIME-TLAG`
	`  ENDIF`
	
	`; Plasma concentration`
	`  EXPKA=EXP(-KA*TAD)`
	`  EXPKE=EXP(-KE*TAD)`
	`  CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)`
	
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`  CE=CP`
	`  PCA=E0 + EMAX*CE/(C50+CE)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
		Note that DOSE must be defined on every record so it is obtained 'on the fly' from the AMT value. The AMT value is only >0 at TIME=0.

Slide 13	**Warfarin Immediate**  	Individual 'post hoc' predictions from the immediate effect model describe most of the time course of PCA but in general the time of the predicted greatest effect is earlier than the observed effect.
Slide 14	**Warfarin Immediate**  	Individual 'post hoc' predictions from the immediate effect model describe most of the time course of PCA but in general the time of the predicted greatest effect is earlier than the observed effect.
Slide 15	**Delayed Effect** **Effect Compartment Model** • Two Basic Approaches – PREDPP • ADVAN4 Very small peripheral compartment • ADVAN6 Differential Equations – $PRED • Write model for CP and CE 	The visual predictive check points to using a model with a delayed effect. The simplest form of delayed effect model uses an effect compartment. This is usually considered an empirical model but if the delay in effect is only a few minutes then it might be a reasonable way to described the time course of drug distribution from plasma to the site of action in an organ. $PRED and ADVAN6 can be used to write exact solutions to the effect compartment model. Because ADVAN6 has to solve differential equations it is slower. ADVAN4 can be used by making the peripheral compartment have a negligible volume. This is helpful for complex dosing histories that would be hard to code in $PRED.

Slide 16	**Effect Compartment Using ADVAN4**
	
	`$SUB ADVAN4 TRANS4`
	`$PK`
	`; Define LN2`
	`IF (NEWIND.EQ.0) THEN`
	`  LN2=LOG(2)`
	`ENDIF`
	
	`; Define parameters`
	`  KA=LN2/TABS`
	`  ALAG1=TLAG`
	`  S2=V`
	`  V2=V`
	`KEQ=LN2/TEQ`
	`V3=V2*0.0001 ; negligible volume`
	`Q=V3*KEQ`
	
	`$ERROR`
	`  CP=A(2)/V2`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	`CE=A(3)/V3`
	`PCA=E0 + EMAX*CE/(C50+CE)`
	`IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`ENDIF`
	
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		Note how the peripheral compartment volume is scaled to be a very small fraction (0.0001) of the central compartment volume. This ensures it will have a negligible influence on the model predictions for the central compartment concentrations.

Slide 17	**Effect Compartment Using ADVAN6**
	
	`$SUBR ADVAN6 TOL=9`
	`$MODEL`
	`  COMP (GUT)`
	`  COMP (CENTRAL)`
	`  COMP (EFFECT)`
	
	`$PK`
	`; Define LN2`
	`  IF (NEWIND.LE.1) THEN`
	`  LN2=LOG(2)`
	`  ENDIF`
	`; Define parameters`
	`  KA=LN2/TABS`
	`  ALAG1=TLAG`
	`  S2=V`
	`  KEQ=LN2/TEQ`
	
	`$DES`
	`  GUT=A(1)`
	`  DCP=A(2)/V`
	`  DCE=A(3)`
	
	`  RATEIN=KA*GUT`
	`  DADT(1)= -RATEIN`
	`  DADT(2)= RATEIN - DCP*CL`
	`  DADT(3)= KEQ*(DCP - DCE)`
	
	`$ERROR`
	`  CP=A(2)/V`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`  CE=A(3)`
	`  PCA=E0 + EMAX*CE/(C50+CE)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
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		The solution to differential equation 3 is scaled in terms of concentration. There is no need to define a volume of this compartment. It has no meaning for this model.

Slide 18	**Effect Compartment Using $PRED**
	
	`$PRED`
	`; Get DOSE from AMT`
	`  IF (NEWIND.LE.1) THEN`
	`  LN2=LOG(2)`
	`  DOSE=0`
	`  ENDIF`
	`  IF (AMT.GT.0) DOSE=AMT`
	
	`; Define parameters`
	`  KA=LN2/TABS`
	`  KE=CL/V`
	`  KEQ=LN2/TEQ`
	
	`; Adjust time for lagtime`
	`  IF (TIME.LE.TLAG) THEN`
	`  TAD=0`
	`  ELSE`
	`  TAD=TIME-TLAG`
	`  ENDIF`
	
	`; Plasma concentration`
	`  EXPKA=EXP(-KA*TAD)`
	`  EXPKE=EXP(-KE*TAD)`
	`  CP=DOSE*KA/(V*(KA-KE))*(EXPKE-EXPKA)`
	`  IF (DVID.LE.1) THEN`
	`  Y=CP*(1+RUV_CV) + RUV_SD`
	`  ENDIF`
	
	`; Effect compartment model concentration`
	`  EXPKQ=EXP(-KEQ*TAD)`
	`  CEEXKE=EXPKE/(KA-KE)/(KEQ-KE)`
	`  CEEXKA=EXPKA/(KE-KA)/(KEQ-KA)`
	`  CEEXKQ=EXPKQ/(KA-KEQ)/(KE-KEQ)`
	`  CE=DOSE*KA*KEQ/V*(CEEXKE+CEEXKA+CEEXKQ)`
	`  PCA=E0 + EMAX*CE/(C50+CE)`
	`  IF (DVID.EQ.2) THEN`
	`  Y=PCA + RUV_FX`
	`  ENDIF`
	
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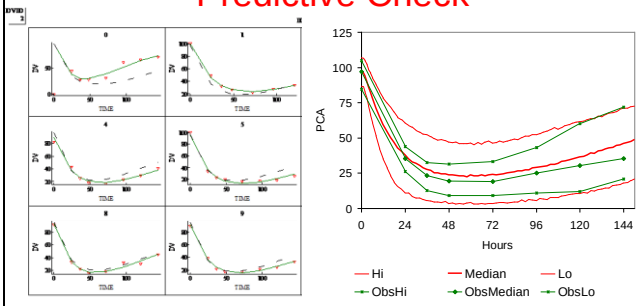
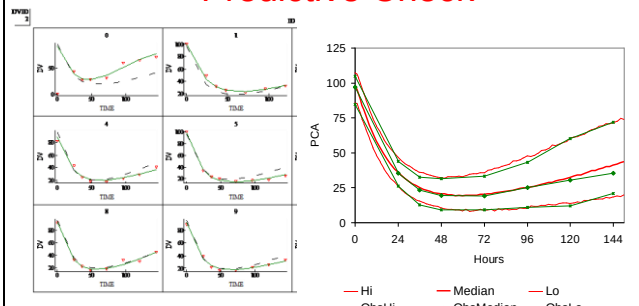
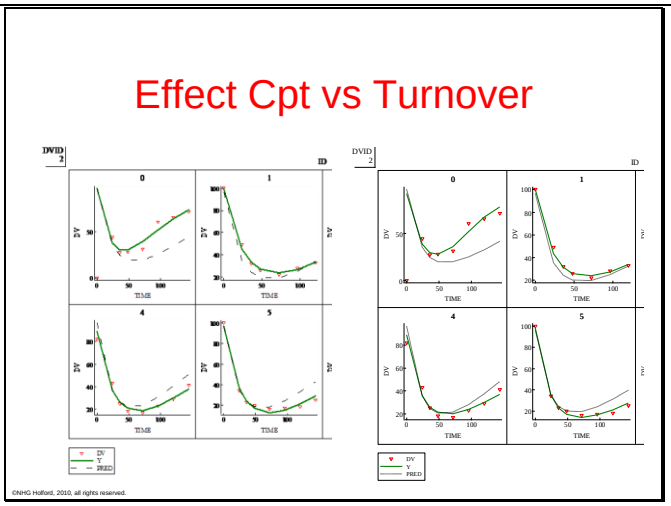
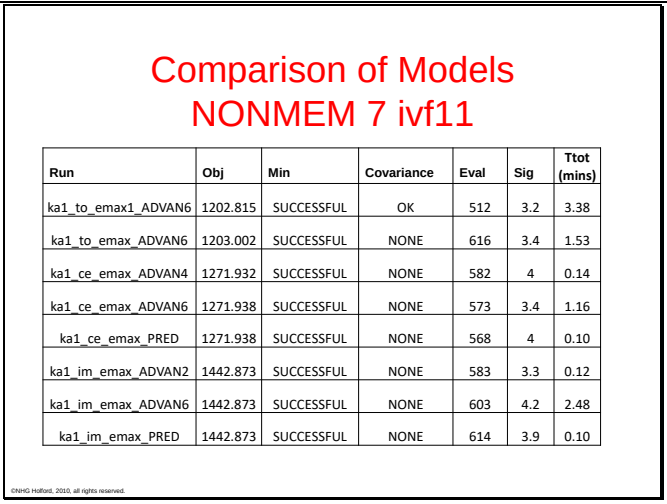
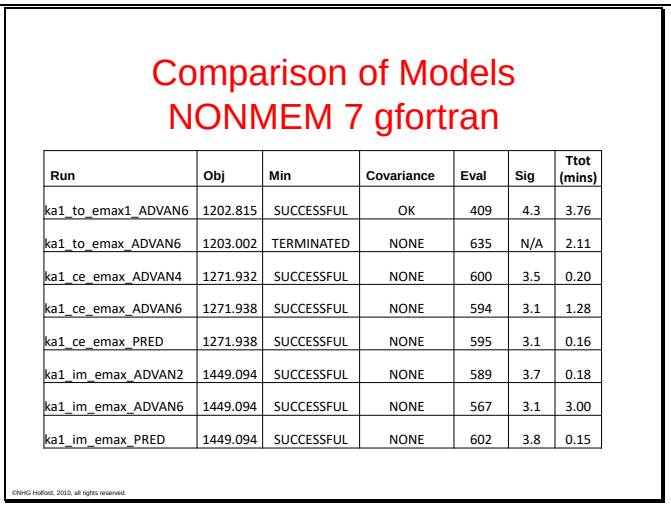
		The effect compartment model for a first-order input one compartment model requires an additional exponential term.

Slide 19	**Warfarin Ce ADVAN4 Predictive Check**  	The individual 'post hoc' predictions are much better than using the immediate model. This model looks fine. But are we missing something? The visual predictive check confirms that the average prediction matches the observed effect time course but the variability is clearly overestimated.

Slide 20	**Turnover Using ADVAN6 NONMEM VI or NONMEM 7**
	`$SUBR ADVAN6 TOL=9`
	`$MODEL`
	`COMP (GUT)`
	`COMP (CENTRAL)`
	`COMP (TRNOVR)`
	`$PK`
	`A_0(3)=E0`
	`;TOVER is turnover half-life`
	`KOUT=LN2/TOVER`
	`RIN=E0*KOUT`
	`$DES`
	`RATEIN=KA*A(1)`
	`DCP=A(2)/V`
	`DPCA=A(3)`
	`PD=1+EMAX*DCP/(C50+DCP)`
	`DADT(1)=-RATEIN`
	`DADT(2)=RATEIN - CL*DCP`
	`DADT(3)=RIN*PD - KOUT*DPCA`
	`$ERROR`
	`CP=A(2)/V`
	`IF (DVID.LE.1) THEN`
	`Y=CP*(1+RUV_CV) + RUV_SD`
	`ENDIF`
	`PCA=A(3)`
	`IF (DVID.EQ.2) THEN`
	`Y=PCA + RUV_FX`
	`ENDIF`
	
		The turnover family of models describe delayed drug effects where the delay is due to the turnover of a physiological mediator. This is well understood as the mechanism of the delay for warfarin.
		NONMEM VI allows initialization of the turnover compartment directly using the special variable A_0().

Slide 21	**Warfarin Turnover Predictive Check**  	The visual predictive check shows that the turnover model describes the variability of the observations much better than the effect compartment model.

Slide 22		The individual “post hoc” predictions from the turnover model do not look any better than the predictions from the effect compartment model.
Slide 23		
Slide 24		Gfortran objective function is higher for immediate models compared with ivf11. Run times are longer than ivf11.

Run	Obj	Min	Covariance	Eval	Sig	Ttot (mins)
ka1_to_emax1_ADVAN6	1202.815	SUCCESSFUL	OK	512	3.2	3.38
ka1_to_emax_ADVAN6	1203.002	SUCCESSFUL	NONE	616	3.4	1.53
ka1_ce_emax_ADVAN4	1271.932	SUCCESSFUL	NONE	582	4	0.14
ka1_ce_emax_ADVAN6	1271.938	SUCCESSFUL	NONE	573	3.4	1.16
ka1_ce_emax_PRED	1271.938	SUCCESSFUL	NONE	568	4	0.10
ka1_im_emax_ADVAN2	1442.873	SUCCESSFUL	NONE	583	3.3	0.12
ka1_im_emax_ADVAN6	1442.873	SUCCESSFUL	NONE	603	4.2	2.48
ka1_im_emax_PRED	1442.873	SUCCESSFUL	NONE	614	3.9	0.10

Run	Obj	Min	Covariance	Eval	Sig	Ttot (mins)
ka1_to_emax1_ADVAN6	1202.815	SUCCESSFUL	OK	409	4.3	3.76
ka1_to_emax_ADVAN6	1203.002	TERMINATED	NONE	635	N/A	2.11
ka1_ce_emax_ADVAN4	1271.932	SUCCESSFUL	NONE	600	3.5	0.20
ka1_ce_emax_ADVAN6	1271.938	SUCCESSFUL	NONE	594	3.1	1.28
ka1_ce_emax_PRED	1271.938	SUCCESSFUL	NONE	595	3.1	0.16
ka1_im_emax_ADVAN2	1449.094	SUCCESSFUL	NONE	589	3.7	0.18
ka1_im_emax_ADVAN6	1449.094	SUCCESSFUL	NONE	567	3.1	3.00
ka1_im_emax_PRED	1449.094	SUCCESSFUL	NONE	602	3.8	0.15

Slide 25

Comparison of Models NONMEM VI

Run	Obj	Min	Covariance	Eval	Sig
ka1_to_emax_ADVAN6	1202.815	Terminated Inf Obj Func	NONE	657	.
ka1_to_emax1_ADVAN6	1202.816	Successful	OK	367	3.1
ka1_ce_emax_ADVAN4	1271.931	Successful	ABORTED	597	3.3
ka1_ce_emax_ADVAN6	1271.936	Successful	ABORTED	539	3.2
ka1_ce_emax_PRED	1271.939	Successful	OK	608	3.2
ka1_im_emax_ADVAN2	1442.809	Successful	ABORTED	1225	3.0
ka1_im_emax_ADVAN6	1442.809	Successful	OK	929	3.0
ka1_im_emax_PRED	1442.809	Successful	ABORTED	1384	3.5

Fixing Emax to 1 allowed the turnover model to finish successfully.
Whether the covariance step runs is not a helpful criterion of model suitability.

Slide 26

Comparison of Parameters NONMEM 7 ivf11

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_to_emax_ADVAN6	96.6	-0.999	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-256	11.1	39.5
ka1_im_emax_ADVAN2	96.5	-74.3	0.221	.
ka1_im_emax_ADVAN6	96.5	-74.3	0.221	.
ka1_im_emax_PRED	96.5	-74.3	0.221	.

The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TOVER estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

Slide 27

Comparison of Parameters NONMEM 7 gfortran

Run	POP S0	POP EMAX	POP C50	POP TEQ/TOVER
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_to_emax_ADVAN6	96.6	-0.999	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-256	11.1	39.5
ka1_im_emax_ADVAN2	96.7	-72.7	0.0875	.
ka1_im_emax_ADVAN6	96.7	-72.7	0.0875	.
ka1_im_emax_PRED	96.7	-72.7	0.0875	.

Gfortran estimate of Emax is higher (less negative) and EC50 are lower than with ivf11

Slide 28

Comparison of Parameters NONMEM VI

Run	POP E0	POP EMAX	POP C50	POP TOVER/ TEQ
ka1_to_emax_ADVAN6	96.6	-1	1.18	13
ka1_to_emax1_ADVAN6	96.6	-1	1.18	13
ka1_ce_emax_ADVAN4	96.7	-256	11.1	39.5
ka1_ce_emax_ADVAN6	96.7	-256	11.1	39.5
ka1_ce_emax_PRED	96.7	-257	11.1	39.5
ka1_im_emax_ADVAN2	96.5	-74.3	0.22	.
ka1_im_emax_ADVAN6	96.5	-74.3	0.22	.
ka1_im_emax_PRED	96.5	-74.3	0.22	.

The half-life of PCA is reported in the literature to be about 14 hours. This is very close to the TOVER estimate of 13 hours from this data set. Notice also the more physiological meaning of an Emax of -1 i.e. 100% inhibition of PCA formation.

Slide 29

Comparison of Random Effects NONMEM 7 ivf11

Run	PPV S0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax1_ADVAN6	0.053	0.000	0.445	0.104	3.82
ka1_to_emax_ADVAN6	0.053	0.000	0.446	0.104	3.83
ka1_ce_emax_ADVAN4	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_PRED	0.051	0.002	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.008	0.010	0.880	.	8.37
ka1_im_emax_ADVAN6	0.008	0.010	0.880	.	8.37
ka1_im_emax_PRED	0.008	0.010	0.880	.	8.37

The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in C50 are more important than the value predicted using the effect compartment model.
Gfortran estimates for immediate models have larger PPV compared with ivf11

Slide 30

Comparison of Random Effects NONMEM 7 gfortran

Run	PPV S0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
ka1_to_emax1_ADVAN6	0.053	0.000	0.445	0.104	3.82
ka1_to_emax_ADVAN6	0.053	0.000	0.446	0.104	3.83
ka1_ce_emax_ADVAN4	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.051	0.002	0.224	0.269	3.81
ka1_ce_emax_PRED	0.051	0.002	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.008	0.025	1.308	.	8.37
ka1_im_emax_ADVAN6	0.008	0.025	1.308	.	8.37
ka1_im_emax_PRED	0.008	0.025	1.308	.	8.37

The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in C50 are more important than the value predicted using the effect compartment model.

Slide 31	**Comparison of Random Effects NONMEM VI** | Run	PPV E0	PPV EMAX	PPV C50	PPV TEQ	RUV FX
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ka1_to_emax_ADVAN6	0.0533	6.54E-07	0.445	0.104	3.82
ka1_to_emax1_ADVAN6	0.0533	0.00E+00	0.445	0.104	3.82
ka1_ce_emax_ADVAN4	0.0510	1.77E-05	0.224	0.269	3.81
ka1_ce_emax_ADVAN6	0.0510	2.93E-06	0.224	0.269	3.81
ka1_ce_emax_PRED	0.0510	1.78E-04	0.224	0.269	3.81
ka1_im_emax_ADVAN2	0.0000	1.73E-02	0.879	.	8.37
ka1_im_emax_ADVAN6	0.0000	1.72E-02	0.878	.	8.37
ka1_im_emax_PRED	0.0000	1.72E-02	0.878	.	8.37 | 	The residual error is very similar for the effect compartment and turnover models. The turnover model suggests that between subject differences in EC50 are more important than the value predicted using the effect compartment model.
Slide 32