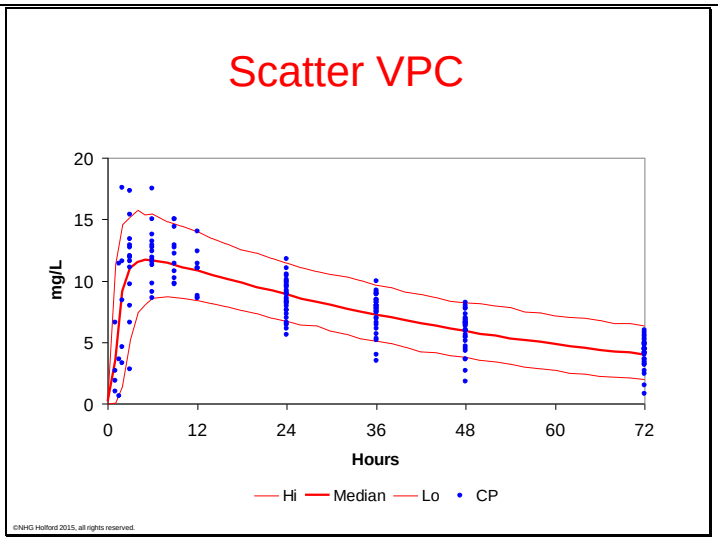
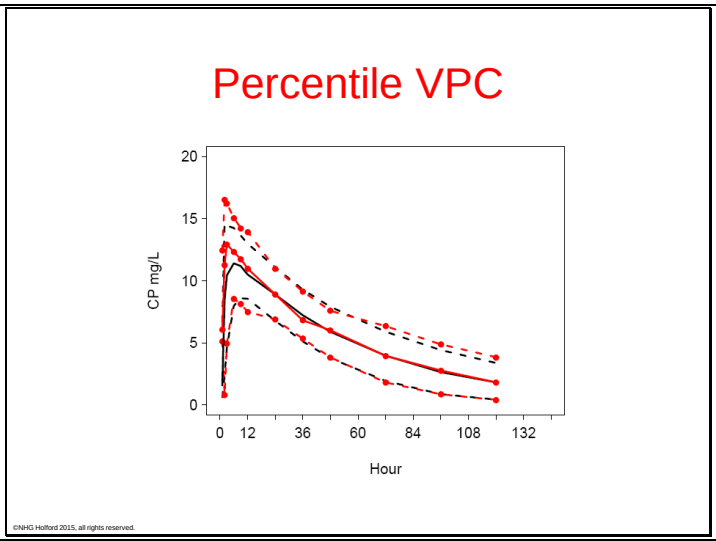
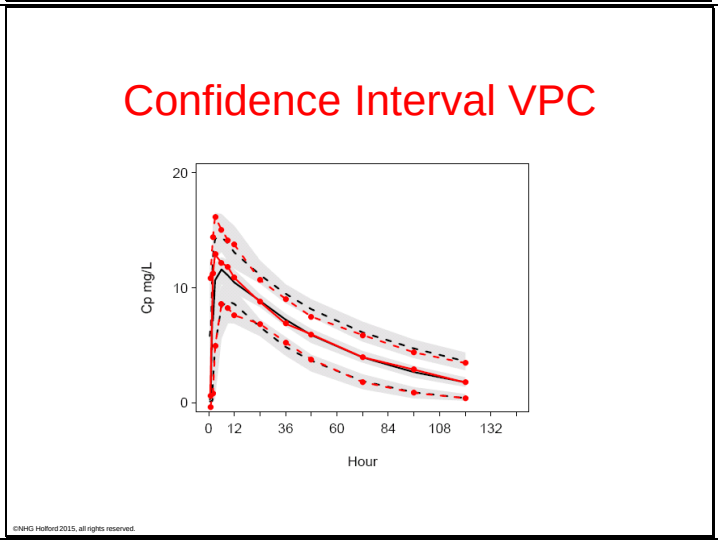
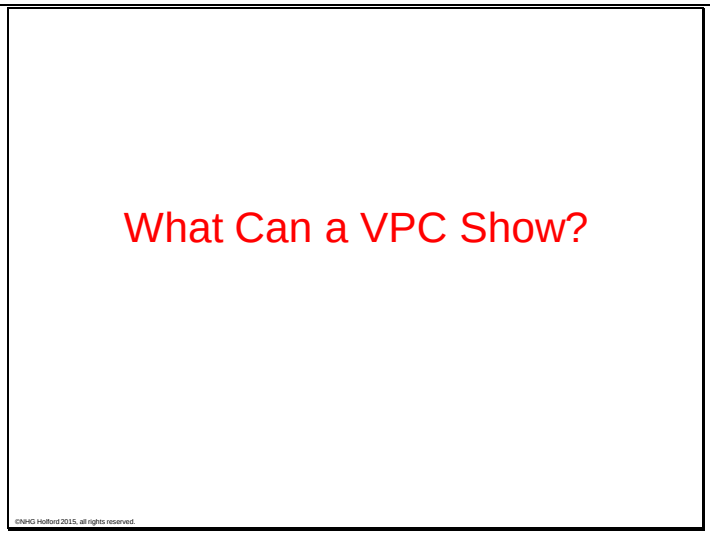
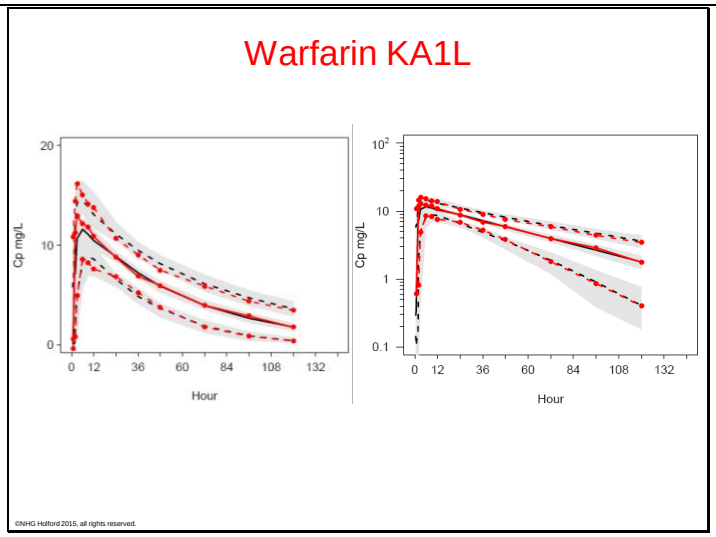
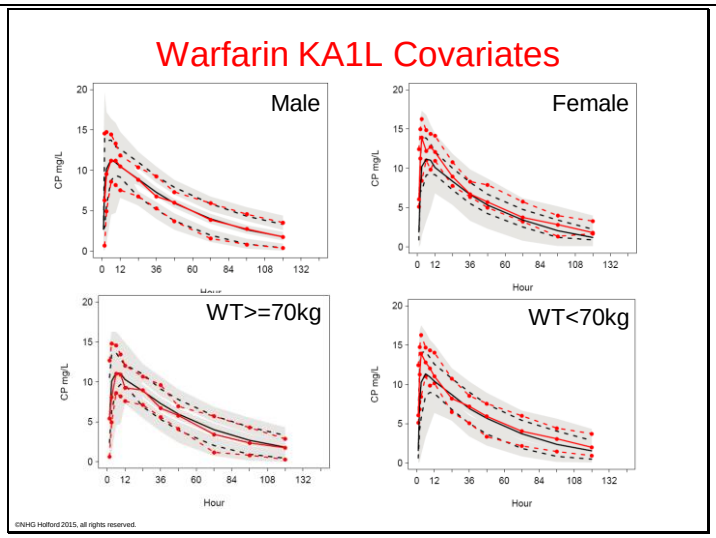
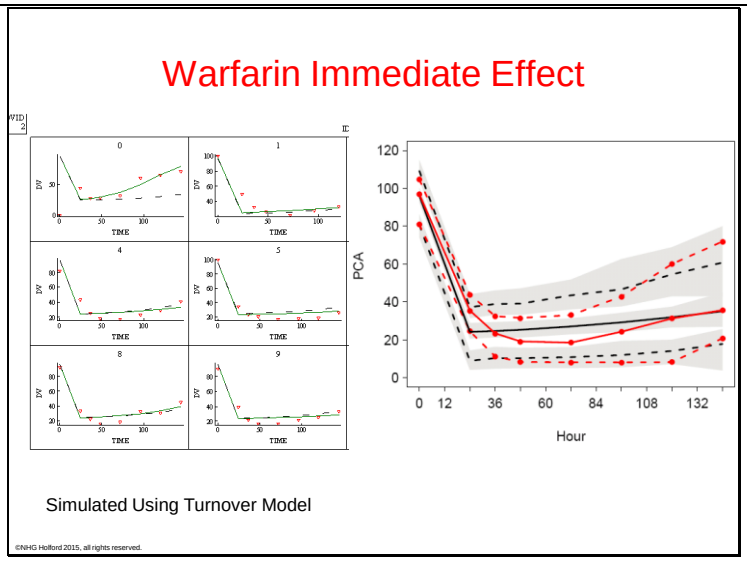
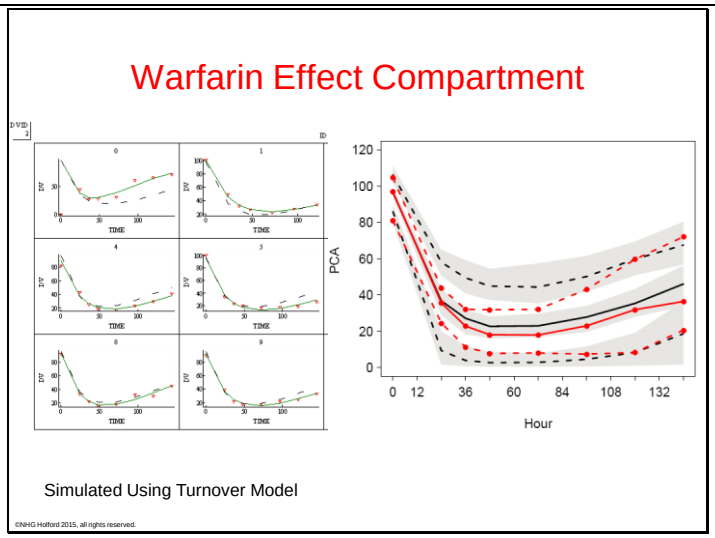
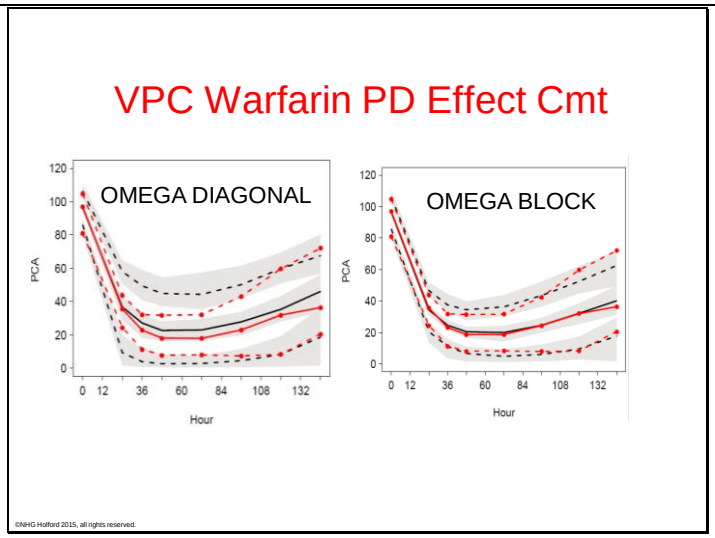
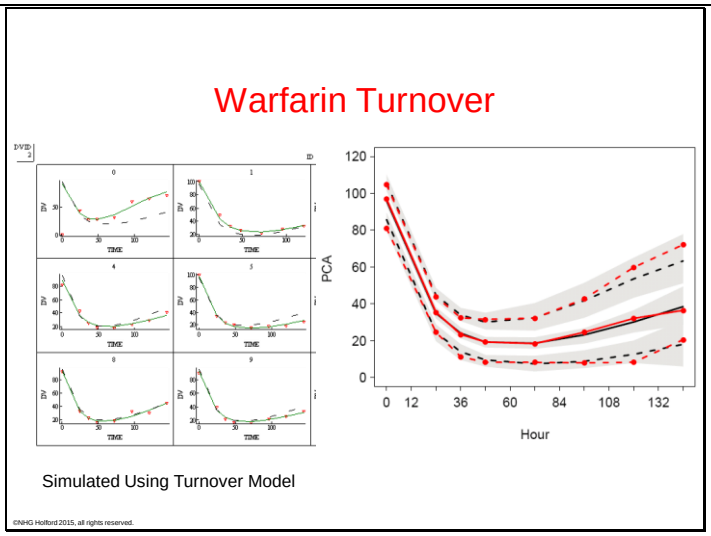
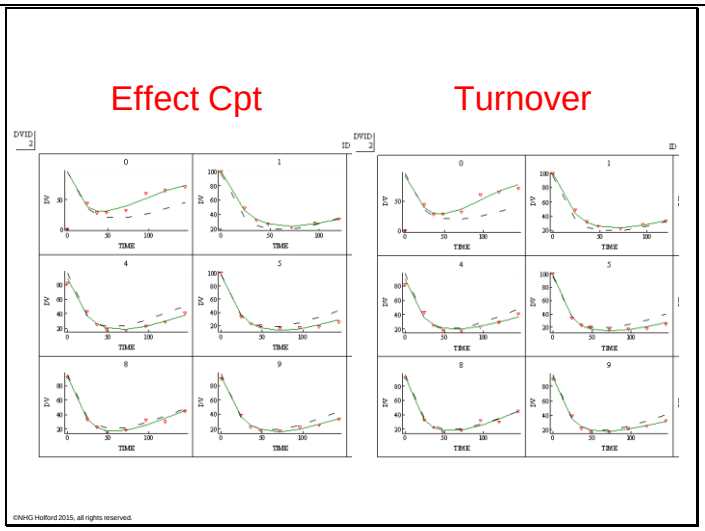
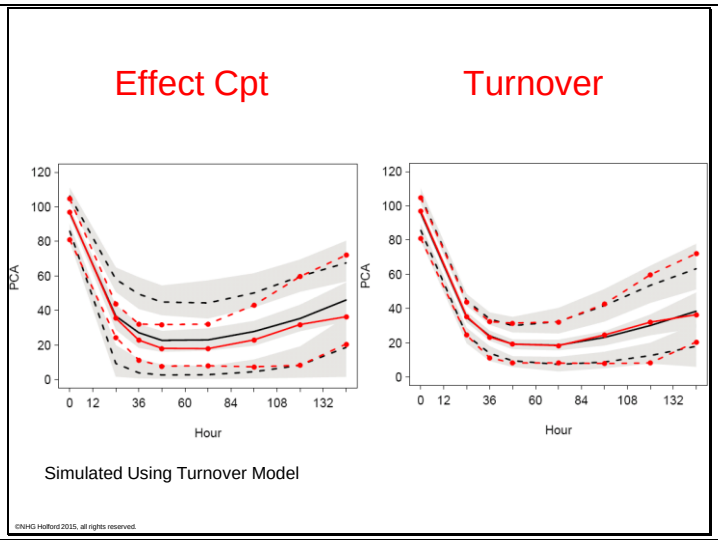
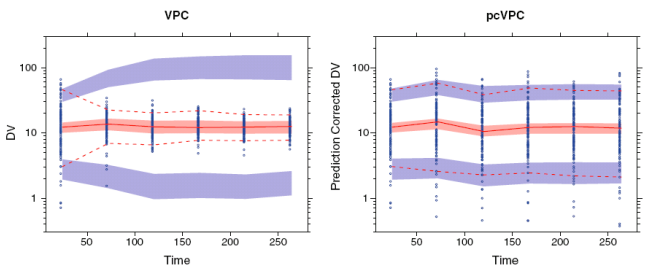
Slide 1	# An Introduction to Visual Predictive Checks Nick Holford Department of Pharmacology & Clinical Pharmacology University of Auckland	
Slide 2	## Outline • What is a Visual Predictive Check? • What choices are there in presentation? • What can it help to show? ©NHG Holford 2015, all rights reserved.	
Slide 3	## What is a VPC? • Graphical Comparison of Observations and Simulated Predictions – Simulated predictions include fixed and random between subject+occasion variability as well as residual error – They are different from 'population' predictions (PRED) (fixed effects without random effects) and individual predictions (IPRED)(empirical Bayes estimates subject to shrinkage) • VPC compares statistics derived from the distribution of observations and the distribution of predictions – E.g. median and 90% intervals at 1 h after the dose – Intervals can be joined together in time sequence to create bands (but most often the bands are called 'intervals') ©NHG Holford 2015, all rights reserved.	VPCs use a different kind of prediction compared with traditional diagnostic plots. They are based on simulations of model predictions including random effects (especially between subject variability (BSV)). Summary measures of the distribution of predictions and observations are compared visually. Typical summary measures are the median and an interval defined by the lower 5% and upper 5% of the values.

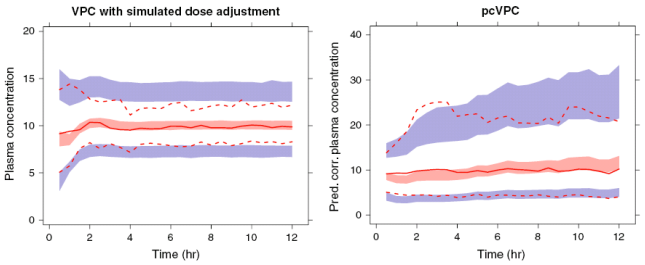
Slide 4	 ©NHG Holford 2015, all rights reserved.	There are several ways of creating VPCs with increasing complexity. In summary there are three basic kinds of VPC. The first is the scatter plot VPC which shows the observations along with some prediction intervals. This is a useful starting point for connecting observations with prediction intervals. However when there is a lot of data the actual distribution of the observations can be hard to appreciate. This naïve scatterplot VPC should be avoided because it does not allow direct visual comparison of the observed and predicted distributions.
Slide 5	 ©NHG Holford 2015, all rights reserved.	The second kind of VPC summarises the distribution of observations with observation intervals so they can be compared directly with the prediction intervals and the medians of the observed and predicted values. The red lines are the observation intervals. The black lines are the prediction intervals. The percentile VPC is easier to interpret when there are lots of observations. It is however difficult to appreciate if the differences between observed and predicted percentiles arise by chance or not.
Slide 6	 ©NHG Holford 2015, all rights reserved.	The third type shows a grey 95% confidence band around each of the prediction intervals obtained by simulation. The confidence intervals give an indication of the uncertainty of the predictions.

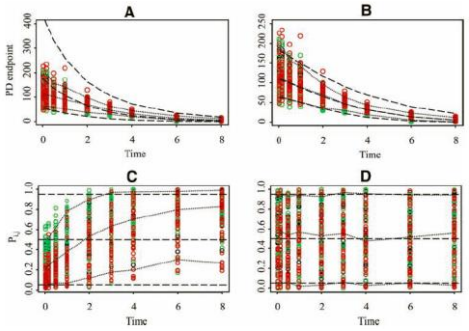
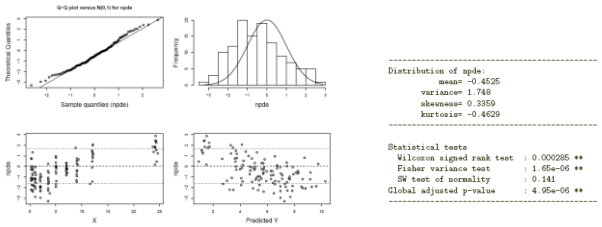
Slide 7		
Slide 8		Note that the peak of the median observation interval seems to lie outside the 95% confidence band for the median (linear concentration scale in left hand plot). This is in an indication of model misspecification describing absorption. The log concentration scale (right hand plot) confirms that the post-absorption phase is well described both in terms of the central tendency (median) but also in terms of the variability (5 and 90% ile intervals).
Slide 9		Stratification of the VPCs by size and sex suggests that either lower weight (<70 kg) or female sex is associated with under-prediction around the peak concentrations.

Slide 10		Data has been simulated from a warfarin PKPD model involving turnover of prothrombin complex activity (PCA) after a single oral dose of warfarin. The PK model is first order absorption and first order elimination from one compartment. The data has been fitted with the same PK model used to simulate the data but the PD model assumes an immediate effect of warfarin plasma concentration on PCA. The left hand plots show individual predictions obtained from empirical Bayes estimates and the corresponding observations. The right hand plot is a percentile VPC with 90% intervals. Both the individual plots and the VPC show poor predictions.
Slide 11		The PD model now assumes a delayed onset of warfarin effect using an effect compartment model for concentrations driving the change in PCA. The individual predictions look very good but the VPC median prediction lies above the median observation from 24 h onwards and the 90% interval is clearly much wider than the observations. This suggests the model is not properly describing the data despite the good individual predictions shown on the left (red symbols are observations, green lines are individual predictions, black lines are group predictions).
Slide 12		Using the wrong random effect covariance structure can appear to correct VPC problem. This means that one cannot rely on internal evaluation using VPC.

Slide 13		Finally we can see what happens when the true model is used to fit the data. When a turnover model is used the individual predictions remain good and the VPC percentile plot looks good as well.
Slide 14		Notice that plots using empirical Bayes estimates for predictions are essentially the same for both the effect compartment and turnover model. Yet the VPCs show the predictions of the effect compartment model are a poorer description of the observations. This is a consequence of shrinkage. The shrinkage for the effect cpt model was 14-44% and for the turnover model was 11-40%. It has been suggested that all parameters must have less than 20% shrinkage in order to draw reliable conclusions from individual plots. However, shrinkage estimates do not take account of the correlation between parameters and it is the correlated set of parameters that determines the prediction. Even if one or more parameters has relatively high shrinkage the individual prediction may be reasonably reliable e.g. for sequential PKPD models using the individual pharmacokinetic parameter (IPP) approach, although other sequential methods are usually better.

Slide 15	 Simulated Using Turnover Model ©NHG Holford 2015, all rights reserved.	This slide compares the VPC using the incorrect effect compartment model with the VPC obtained from the true turnover model. Note that the model is misspecified in terms of the structural model yet the VPC shows marked discrepancies in terms of the predicted variability. Variability differences should not be interpreted as being due to misspecification of the random effects alone. It is reassuring to see that the VPC with the true model has good agreement with the observations.
Slide 16	PRED Corrected VPC Prediction correction (PRED correction) for dependent variable, Y_{ij}, with lower bound, lb_{ij}: $$pcY_{ij} = lb_{ij} + (Y_{ij} - lb_{ij}) \cdot \frac{\widetilde{PRED}_{bin} - lb_{ij}}{PRED_{ij} - lb_{ij}} \quad (1)$$ Prediction correction (PRED correction) for log-transformed dependent variable, $ln(Y_{ij})$: $$\ln(pcY_{ij}) = \ln(Y_{ij}) + \left(\ln\left(\widetilde{PRED}_{bin}\right) - \ln(PRED_{ij})\right) \quad (2)$$ Prediction corrected VPCs attempt to adjust for differences in covariates. A simple form of prediction correction is to dose standardize observed and predicted concentrations. Essential when adaptive dosing occurs e.g. models built from therapeutic drug monitoring data ©NHG Holford 2015, all rights reserved.	Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 2011; 13: 143-51.
Slide 17	Adaptive Dosing Study  **Fig. 2.** Example with *a posteriori* dose adaptation (TDM) based on observed trough plasma concentration (units per liter) monitoring over time. Traditional VPC (*left*) and pcVPC (*right*), with 95% interpercentile range, for the true model applied to a simulated dataset. Graphical interpretation as in Fig. 1 ©NHG Holford 2015, all rights reserved.	A standard VPC without prediction correction shows a big difference between observed and predicted variablity which could be mis-interpreted as meaning there is something wrong with the model. The PRED corrected VPC shows that there is in fact good agreement because the concentrations in each band are standardized for the adaptive dose changes (and other covariates). Note however the PRED correction process distorts both the 'observed' and predicted concentrations with unrealistic 'observations' at later times. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 2011; 13: 143-51.

Slide 18	# An Alternative to pcVPC Simulated Adaptive Dosing  **Fig. 5.** A simulated example where a loading dose was given followed by a constant infusion. The infusion rate was altered to achieve the target concentration of 10 units. The true underlying model is a one-compartment model with autoinduction of CL. A simple one-compartment model without autoinduction has been fitted to the data. The left hand *VPC* has been simulated using the same dose alteration algorithm as in the original study. The *pcVPC* (*right*) have been simulated using only the realized design. Outer percentiles (*dashed red lines*) are 2.5% and 97.5% (95% interpercentile range), the *semitransparent blue fields* are the corresponding model-based confidence intervals, the *solid red line* represents the observed median, and the *semitransparent red field* represents the corresponding model-based confidence interval. The actual observations are not plotted in this picture ©NHG	Simulated adaptive dosing with a standard VPC can be used to confirm the adequacy of the model and the simulation algorithm. The standard VPC does not distort the concentrations like the PRED corrected VPC. Bergstrand M, Hooker AC, Wallin JE, Karlsson MO. Prediction-corrected visual predictive checks for diagnosing nonlinear mixed-effects models. AAPS J 2011; 13: 143-51.
Slide 19	# Prediction Discrepancy 'We evaluate what we call the "prediction discrepancy" (pd) which is defined as the percentile of an observation in the whole marginal predictive distribution under *H*0.' Mentre F, Escolano S. Prediction discrepancies for the evaluation of nonlinear mixed-effects models. J Pharmacokinet Pharmacodyn. 2006 Jun;33(3):345-67. ©NHG Holford 2015, all rights reserved.	The prediction discrepancy method uses stochastic simulation to generate a distribution of predictions for each observation. The percentile of each observation in this distribution is called the prediction discrepancy. The distribution of prediction discrepancies is expected to be uniform if the model correctly predicts the distribution from which the observations came. The prediction discrepancy distribution can be 'normalized' and also take into account correlations of observations within an individual. The resulting normalized prediction discrepancy distribution (NPDE) should have a mean of zero and a standard deviation of 1. Estimates of these parameters can be computed from the NPDE and tested against the null hypothesis that the distribution is ~N(0,1).
Slide 20	# Pseudoresidual Predictive Checks • Standardized VPC But "As Wang and Zhang[1] point out themselves, what they call standardized visual predictive check (SVPC) is nothing other than the prediction discrepancies (pd) named that way, after being called pseudoresiduals by Mentré and Escolano in 2006.[4] It is therefore misleading to present SVPC as something novel when in fact it goes back to something that our group has published and presented in conferences." Comets et al. 2011 • Normalized Prediction Distribution Errors – Prediction discrepancy is adjusted to account for within individual correlations But "we made a case of using pd instead of npde to plot diagnostic graphs because the decorrelation tends to blur the relationship with time when used for visual diagnostics" Comets et al. 2011 ©NHG Holford 2015, all rights reserved.	Note that these kinds of checks are based on testing statistical distribution assumptions rather than evaluating how well observation and predictions agree. Mentre F, Escolano S. Prediction discrepancies for the evaluation of nonlinear mixed-effects models. J Pharmacokinet Pharmacodyn 2006; 33: 345-67. Wang DD, Zhang S. Standardized Visual Predictive Check Versus Visual Predictive Check for Model Evaluation. The Journal of Clinical Pharmacology 2011a; DOI 10.1177/0091270010390040 Comets E, Brendel K, Mentré F. Why Should Prediction Discrepancies Be Renamed Standardized Visual Predictive Check? The Journal of Clinical Pharmacology 2011.

Slide 21	# Standardized VPC "The key difference between SVPC and pd/npde is the focus of the analysis. SVPC evaluates the observation percentile distribution along the time course, whereas pd/npde focuses on the global statistical test without considering the time factor." Wang & Zhang. 2011b  Figures from Wang & Zhang 2011a ©NHG Holford 2015, all rights reserved.	Wang & Zhang claim the standard VPC would have rejected the true model (B and D). But they use scatterplot VPCs without confidence intervals (A and B) which are hard to interpret because of the (unnecessary) overlay of observations. The standardized VPC (SVPC) (C and D) necessarily removes all information about the concentration scale so that model evaluation is missing important information. Wang DD, Zhang S. Standardized Visual Predictive Check Versus Visual Predictive Check for Model Evaluation. The Journal of Clinical Pharmacology 2011a; DOI 10.1177/0091270010390040 (Published on line before Wang & Zhang 2011a). Wang DD, Zhang S. Author's response to Comets et al. The Journal of Clinical Pharmacology 2011b; DOI: 10.1177/0091270011427555.
Slide 22	# NPDE ## Normalised Prediction Distribution Errors  Distribution of npde: mean= -0.4525 variance= 1.748 skewness= 0.3359 kurtosis= -0.4629 Statistical tests Wilcoxon signed rank test : 0.000285 ** Fisher variance test : 1.65e-06 ** SW test of normality : 0.141 Global adjusted p-value : 4.95e-06 ** *Figure 6: graphs plotted by the package, for V_{false} (see legend of figure 4 for a description)* Comets, E., K. Brendel, and F. Mentré, *Computing normalised prediction distribution errors to evaluate nonlinear mixed-effect models: The npde add-on package for R. Computer Methods and Programs in Biomedicine, 2008.* ***90(2): p. 154-166.*** ©NHG Holford 2015, all rights reserved.	The NPDE tests for differences from a perfect fit of the model to the data. Because all models are wrong it is unrealistic to expect a perfect fit. When there is a lot of data the NPDE is sensitive to differences that have no practical relevance. This means it can be considered overpowered and will lead to rejection of the null hypothesis when the model is in fact adequate for purpose. An equivalence type of hypothesis test (such as that used for bioequivalence) is an obvious extension of the method to make it more practically useful as an acceptance method. Note that the scatterplots are of limited value. They would be more informative if percentiles were plotted and joined to show trends.

Slide 23	## How To Do A VPC • Simulate Data – Can be the hardest part – Simulation times (binning)? – How to simulate covariates? • Group (“bin”) Simulated Predictions at each time – Needs some programming • Group (“bin”) Observations at each time – Needs some programming ©NHG Holford 2015, all rights reserved.	There are 3 steps involved in creating a VPC. The first step is to simulate from the model to produce predictions. This step typically requires user intervention for every dataset that is being studied. The next two steps can usually be automated with procedures that are the same for all problems. A convention is needed to identify the independent and dependent variables (especially when there is more than one type of observation e.g. Concentrations and efffects).
Slide 24	## nmvpc • WFN command – nmvpc.bat • R scripts – nmvpc_PKPD.R – nmvpc_PKPD_Functions.R • R scripts can be run directly using R • nmvpc helps to automate repetitive features of doing VPC e.g. with covariate selection ©NHG Holford 2015, all rights reserved.	

Slide 25	## VPC Using WFN and R
	• WFN modification
	– Include path to R.exe in wfn.bat
	`:orgpath`
	`rem ******* Set up Paths to Other Software ******`
	`rem If you use R then set RPATH`
	`set RPATH=C:\Apps\R-2.14.2\bin\i386`
	`rem ******* End Check this ********`
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Slide 26

NM-TRAN

```
$PK
; simulation start
OBS=DV
; simulation end

[Usual $PK (or $PRED) code]

;Simulation Start
REP=IREP ; Replication number
; Create size category based on weight
IF (WT.LT.70) THEN
 SIZE=1
ELSE
 SIZE=2
ENDIF
;must produce NONMEM table file with REP,ID,TIME,DVID,DV,MDV,PRED
;add SEX and SIZE variables to the table file for covariate VPCs
$TABLE REP ID TIME DV PRED OBS MDV DVID SEX SIZE
NOAPPEND ONEHEADER NOPRINT FILE=vpc.fit
$SIM (20120402) ONLYSIM NSUB=100
```

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Slide 27

nmvpc.bat – Model and Names

```
:nonmem
rem set runNONMEM=y to execute nmgo for each model
set runNONMEM=y

rem Set list of models to be simulated e.g. set models=mdl1
mdl2 mdl3
set models=ka1_im_emax_est ka1_ce_emax_est ka1_to_emax1

rem Names of variable in NONMEM table file to be used for the
VPC x-axis
rem This can be used for evaluating continuous covariates e.g.
rem set xnames=TIME TAD WEIGHT for total time, time after dose
and weight
set xnames=TIME

rem Set list of names according to observation type e.g. set
obsnames=CP PCA
set obsnames=CP PCA

goto models
```

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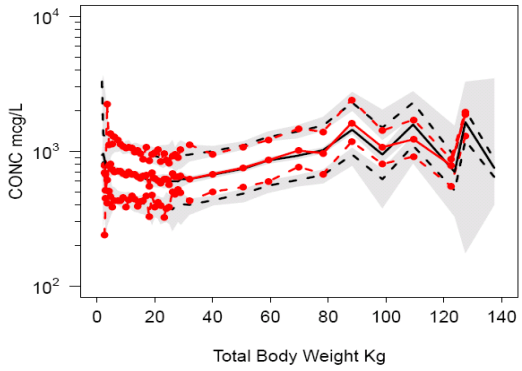
Slide 28

Continuous Covariate VPC



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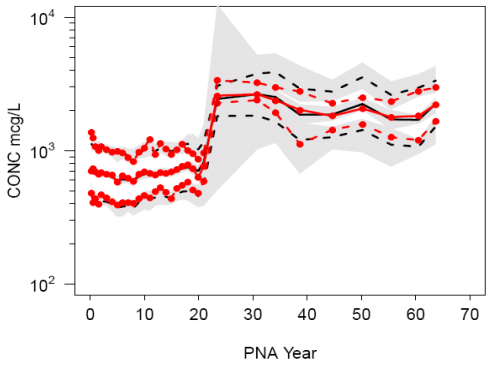
Slide 29

Continuous Covariate VPC



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Slide 30

nmvpc.bat - Observations

```
rem *************************
rem OBSERVATION TYPES SECTION
rem *************************
:obstype
rem Each observation type may have its own
properties
rem The dvid variable is required to distinguish
types

rem Define R script variables for each
observation type
rem No spaces are allowed in variable values.
rem Use '#' which will be replaced by a blank in
xlabel and ylabel values

rem **** COMMON ******
rem Variables common to all observation types
rem Any of these variables may be observation
(obsname) specific

rem List of times for binning observed and
predicted values
set bintimes=c(seq(0,10,1),seq(12,144,12))

set logaxis=
set xlabel=Hour
set xmin=0
set xmax=144
set xtick=12
set lloq=0

rem obsname labels must correspond to names in
the obsnames list
rem A obsname label must have a ":" before the
obsname e.g. :CP for obsname=CP

goto %obsname%

rem **** OBSERVATION SPECIFIC ******
rem user defined obsname labels identify
variables for each observation type

:CP
set dvid=1
set ylabel=%obsname%#mg/L
set ymin=0
set ymax=20
set ytick=5

goto select

:PCA
set dvid=2
set ylabel=%obsname%#%
set ymin=0
set ymax=120
set ytick=20

goto select
```

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Slide 31

nmvpc.bat - Covariates

```
rem ******************************
rem CATEGORICAL COVARIATES SECTION
rem ******************************

:covariate
rem Covariate selection is optional. For VPC
without covariates: set covariates=
rem Set list of covariates (upto 3)  e.g. set
covariates=SEX SIZE
rem Names in the covariates list must match
exactly the names in the simulation table file
set covariates=SEX
rem Each covariate name must be matched with a
list of numeric values for the covariate
rem which will be used to create VPCs for each
value
rem select on covariate 1 e.g. sex values 0 1
set covlist1=0 1
rem select on covariate 2 e.g. size values 1 2
set covlist2=
rem select on covariate 3 e.g. race values 1 2 3
set covlist3=

goto gotcov
```

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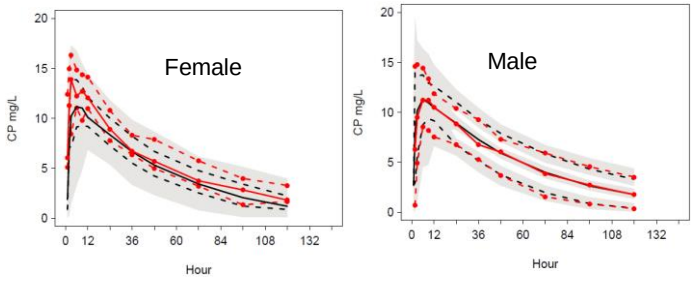
Slide 32

Categorical Covariate



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Slide 33

nmvpc.bat - Options

```
rem Some miscellaneous variables that are rarely changed

rem Percentile range for prediction and confidence
intervals
set PIpercentile=0.9
set CIpercentile=0.95
rem if isstd=y then create standard VPCs
set isstd=y
rem if ispc=y then create pred-corrected VPCs
set ispc=y
rem if iscsv=y then write csv files with numerical values
used for plots
set iscsv=n
rem if isbig=y then re-read simulation file each time to
use less memory
set isbig=n
rem use this to scale TIME variable (e.g. timescale=52 to
scale years to weeks)
set timescale=1
rem if hasmdv=y then use MDV data item to select valid
observations otherwise all records are valid observations
set hasmdv=y
rem Name for MDV item for predictions. If blank then item
name will be the same as for observations (MDV).
set mdvpname=

rem name of R script for VPC (without extension)
set orgR=vpc
```

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Slide 34

Parkinson Study Group DATATOP Cohort

Deprenyl and Tocopherol Antioxidative Therapy of Parkinsonism

PKPD of anti-parkinsonian treatment and Parkinson's disease over 7 years in 800 patients

The Parkinson Study Group. Effect of deprenyl on the progression of disability in early Parkinson's disease. The New England Journal of Medicine 1989;321:1364-1371

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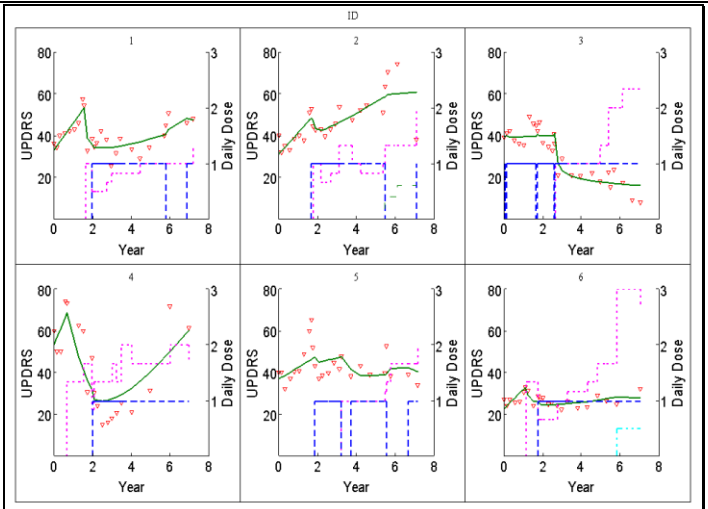
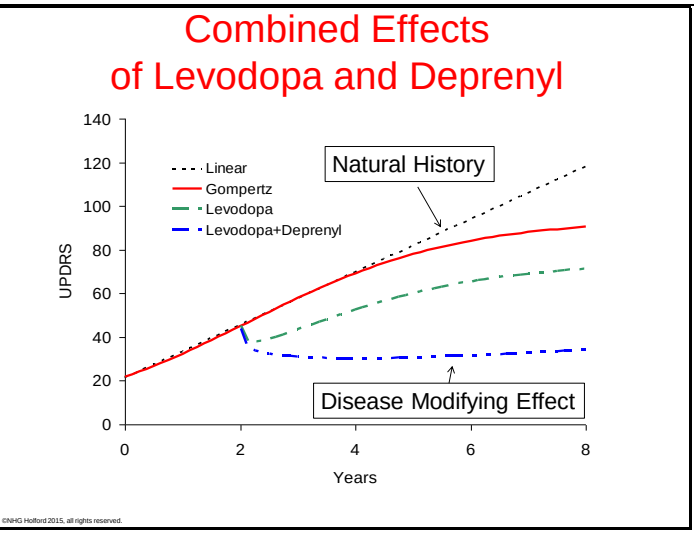
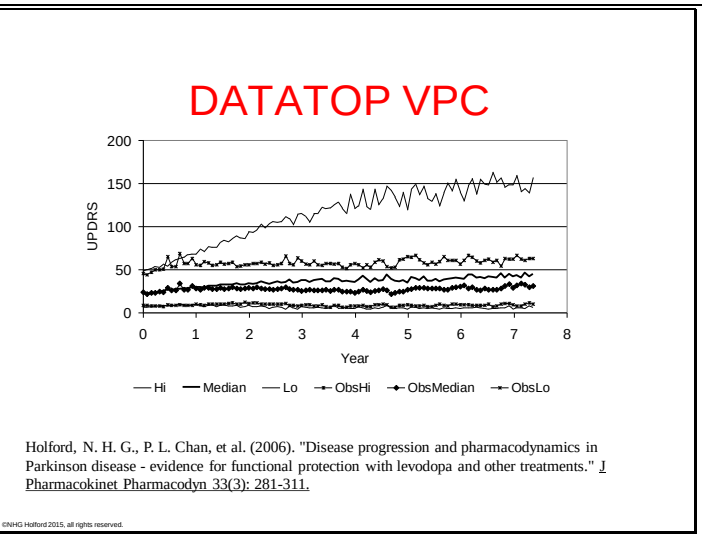
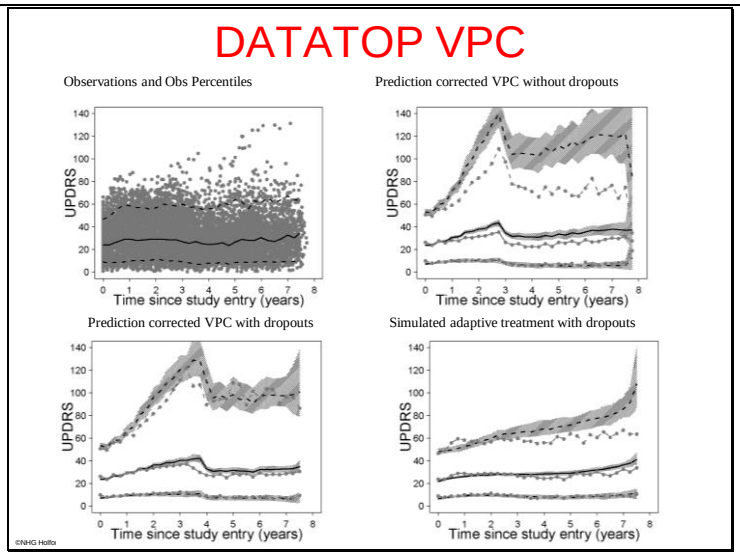
The DATATOP study was performed over 2 year period but patients enrolled in the study were subsequently followed up for 8 years. The time course of disease status in Parkinson's disease and the effects of treatment were described by a disease progress model. The NM-TRAN code for this analysis can be found in Holford et al. 2006.
Holford NHG, Chan PL, Nutt JG, Kieburtz K, Shoulson I. Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments. J Pharmacokinet Pharmacodyn. 2006 Jun;33(3):281-311.

Slide 35	 ©NHG Holford 2015, all rights reserved.	Disease status was followed with the Unified Parkinson's Disease Response Scale (UPDRS). The UPDRS patterns were quite variable from patient to patient. A major source of variability was the response to individual drug treatments.
Slide 36	 ©NHG Holford 2015, all rights reserved.	The effects of levodopa and deprenyl are shown. Both have offset effects and protective effects which was described by an action on the time constant of a Gompertz asymptotic model. See Holford et al 2006 for details of the model code.
Slide 37	 Holford, N. H. G., P. L. Chan, et al. (2006). "Disease progression and pharmacodynamics in Parkinson disease - evidence for functional protection with levodopa and other treatments." J Pharmacokinet Pharmacodyn 33(3): 281-311. ©NHG Holford 2015, all rights reserved.	

Slide 38		Visual Predictive Check showing (A) observations and observed percentiles, (B) prediction corrected VPC without dropouts and (C) with dropouts, and (D) simulated adaptive treatment with dropouts, Median (solid lines) and 90% prediction intervals (dash-lines) of the observed (joined solid circle lines) and simulated data are shown. The confidence intervals for the median and the prediction intervals are shown in plot as shaded bands. Vu TC, Nutt JG, Holford NHG. Progression of motor and nonmotor features of Parkinson's disease and their response to treatment. Br J Clin Pharmacol 2012; 74: 267-83.
Slide 39	Backup ©NHG Holford 2015, all rights reserved.	
Slide 40	nmvpc_PKPD.R - 1 ©NHG Holford 2015, all rights reserved.	

```
### The following items may be modifed by nmVPC.bat

###  NMTBL and NMDIR are changed by nmvpc.bat using WFN environment variables
ISWFN     = T # NONMEM simulation table file: T= Look in Wings for NONMEM run
directory; F = Look in current directory
NMTBL     = ".fit" # NONMEM table file extension
if (ISWFN) NMDIR=".reg"

#Identify Simulation File
modelName = "ka1_to_emax1_simln"       # No file extension

PIpercentile = 0.9  # Percentile for prediction intervals
CIpercentile = 0.95  # Percentile for confidence intervals

logaxis = "" # choose axis for log scale (use "x", "y", "xy" or "")

# bin simulated values by time intervals based on nominal binning times (only
used if binsim=T)
binTimes = c(c(seq(0,10,1),seq(12,144,12)))
Xlabel  = "Hour" # X-axis label on graph
Xmin    =   0 # minimum scale for x-axis
Xmax    = 144 # maximum scale for x-axis
Xtick   =  24 # ticks on x-axis at these intervals for linear scale
```

Slide 41

nmvpc_PKPD.R - 2

```
thisDVID=  1 # #identify observation type using the DVID variable in the simulation and
observation data files
hasDVID =  T # T if observation and simulation data file have DVID data item (otherwise no
selection of DVID)
hasMDV  =  T # T if observation and simulation data file have MDV data item (otherwise all records
are valid DV)
Ylabel  = "mg/L" # Y-axis label on graph
Ymin    =  0 # minimum scale for y-axis
Ymax    = 20 # maximum scale for y-axis
Ytick   = 5 # ticks on y-axis at these intervals for linear scale
LLOQ    = 0 # lower limit of quantitation to apply to predicted values
pdfTxt  = "CP" # pdf file name identifier e.g. use with select

figOutputDir = "vpc_CP.pdf/" # directory for VPC pdf and csv files
timeScale    = 1 # use this to scale TIME variable (e.g. 52 to scale years to weeks)
isSTD        = T # create standard VPC
isPC         = T # create pred-corrected VPC
isCSV        = F # if iscsv=T then write csv files with numerical values used for plots
```

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nmvpc_PKPD.R - 3

```
###  The following items may only be changed here in the R script

binsim    = T # T if simulation times are not the same for every subject (Otherwise use
times in simulation file 'as is')
hasATIM   = F # T if simulation data file has an actual observation time item in the
simulation file (otherwise ATIM=TIME)
hasLLOQ   = T # T if values less than LLOQ should be ignored
plotCI    = T # T if plot confidence intervals
plotPI    = T # T if plot prediction intervals
addLegend = T # T if add a legend to the plot
omitNeg   = T # T if omit negative simulated values

#output options
isPDF        = T # T if generate PDF output otherwise display plots on screen
#pCols       = c(obscol='gray50',simcol='black',pici='gray30')
pCols        = c(obscol='red',simcol='black',pici='gray90') # 0 is black; 100 is white
```

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Slide 43

nmvpc_PKPD.R - 4

```
#Do not change the next line!
#SELECT specific observations e.g. study number
obsFile = obsFile[obsFile$SEX==1,]
simFile = simFile[simFile$SEX==1,]
```

The covariate selection process can be automated with nmvpc.bat

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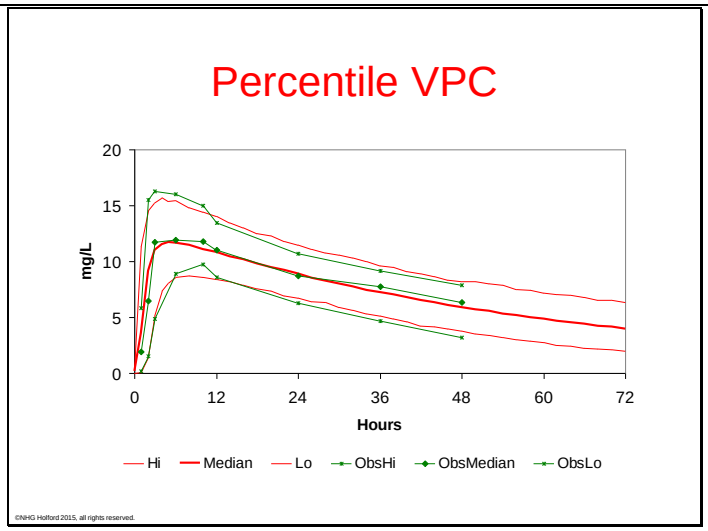
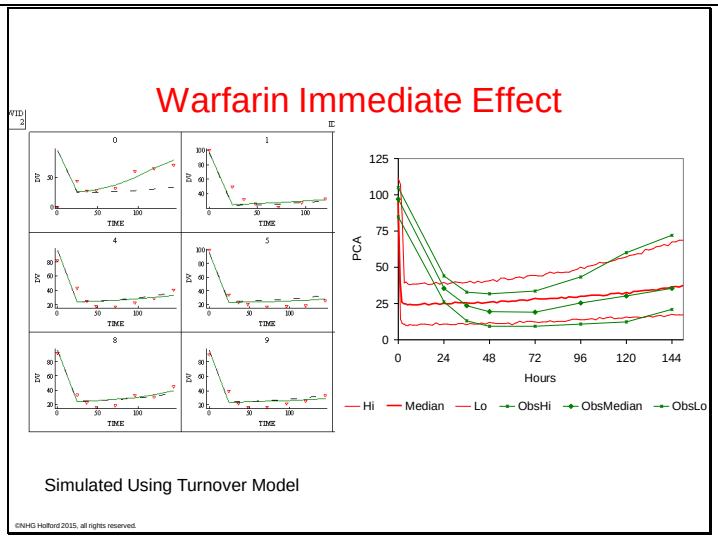
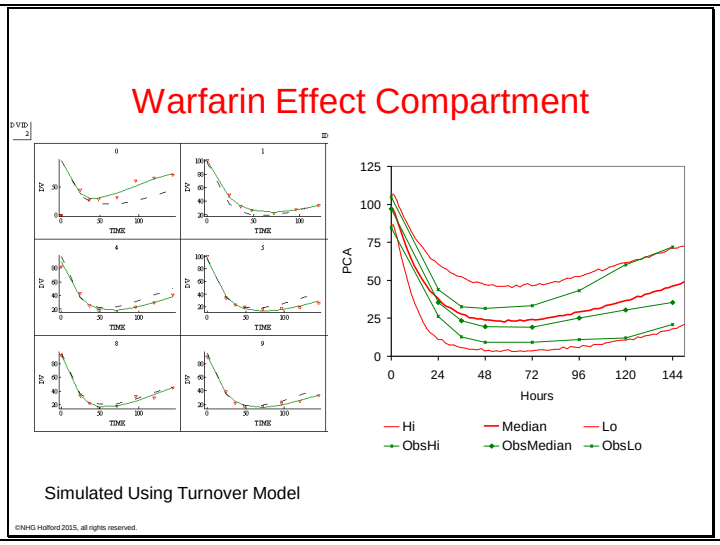
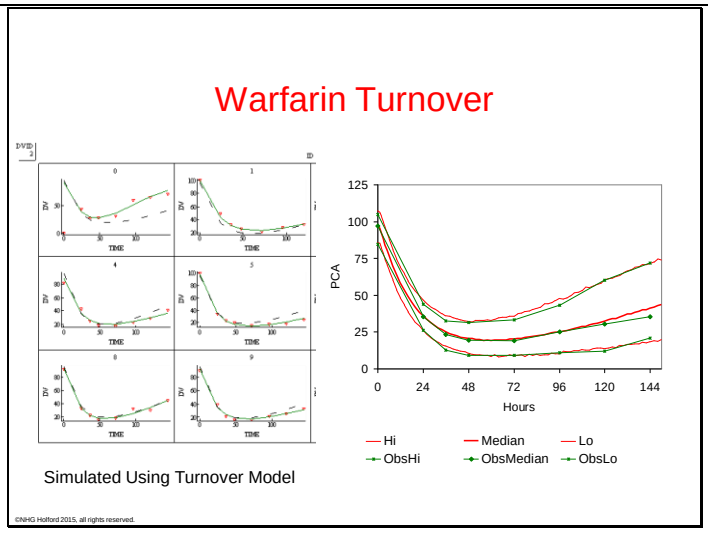
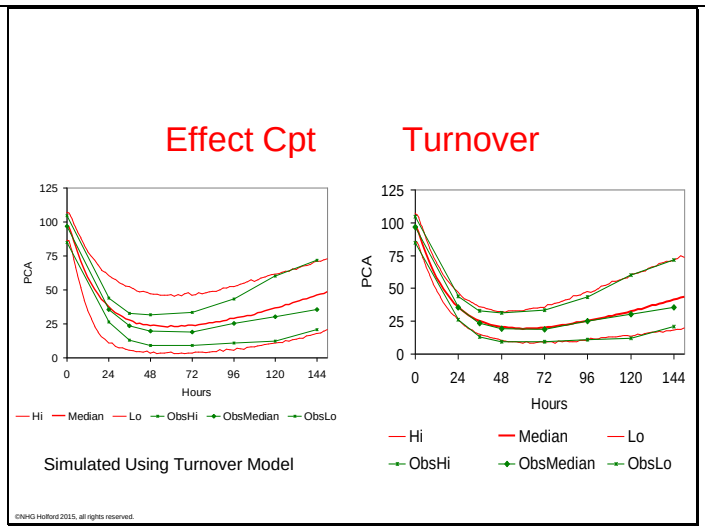
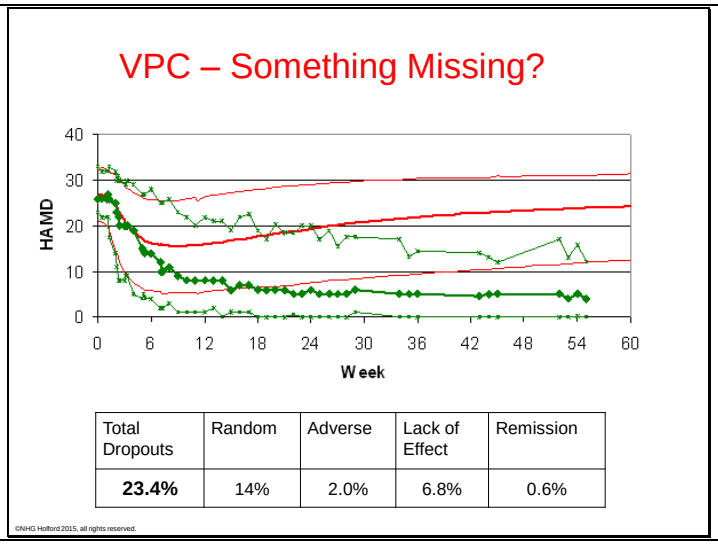
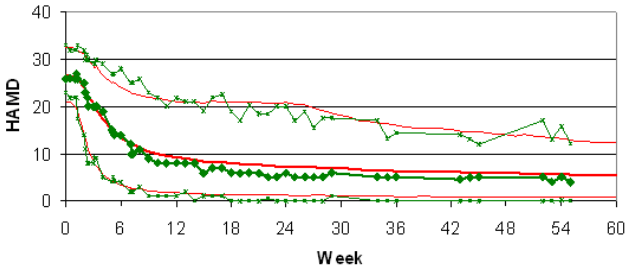
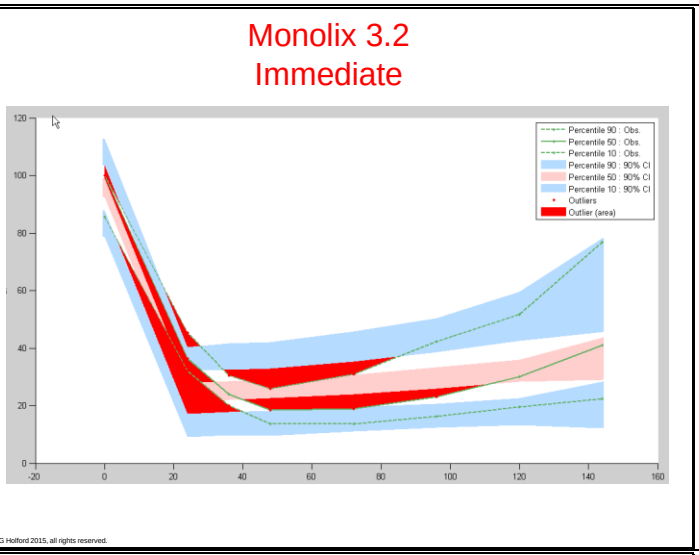
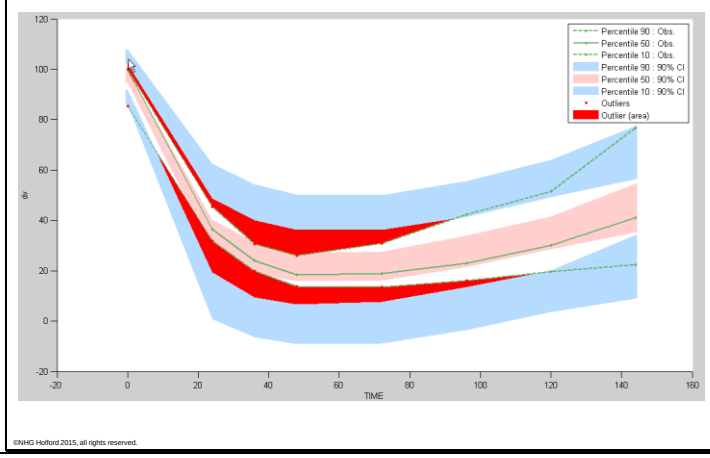
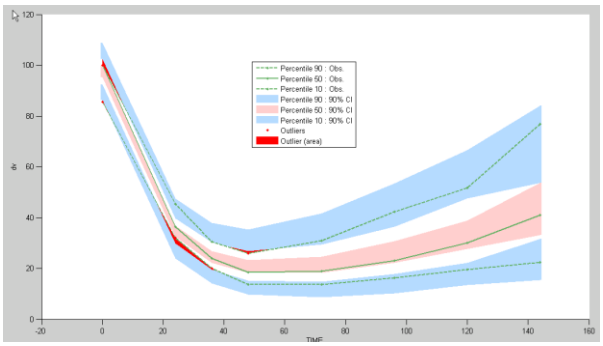
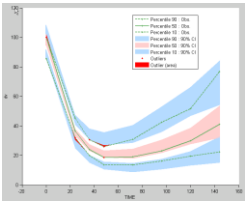
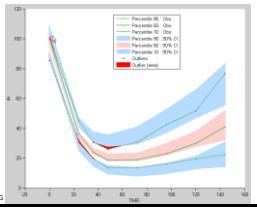
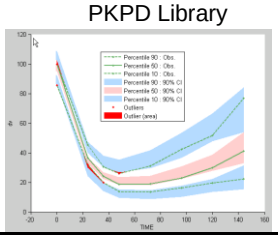
Slide 44	 ©NHG Holford 2015, all rights reserved.	The second kind of VPC summarises the distribution of observations with observation intervals so they can be compared directly with the prediction intervals and the medians of the observed and predicted values. The percentile VPC is easier to interpret when there are lots of observations.
Slide 45	 ©NHG Holford 2015, all rights reserved.	Data has been simulated from a warfarin PKPD model involving turnover of prothrombin complex activity (PCA) after a single oral dose of warfarin. The PK model is first order absorption and first order elimination from one compartment. The data has been fitted with the same PK model used to simulate the data but the PD model assumes an immediate effect of warfarin plasma concentration on PCA. The left hand plots show individual predictions obtained from empirical Bayes estimates and the corresponding observations. The right hand plot is a percentile VPC with 90% intervals. Both the individual plots and the VPC show poor predictions.
Slide 46	 ©NHG Holford 2015, all rights reserved.	The PD model now assumes a delayed onset of warfarin effect using an effect compartment model for concentrations driving the change in PCA. The individual predictions look very good but the VPC median prediction lies above the median observation from 24 h onwards and the 90% interval is clearly much wider than the observations. This suggests the model is not properly describing the data despite the very good individual predictions.

Slide 47		Finally we can see what happens when the true model is used to fit the data. When a turnover model is used the individual predictions remain good and the VPC percentile plot looks good as well.
Slide 48		This slide compares the VPC using the incorrect effect compartment model with the VPC obtained from the true turnover model. It is reassuring to see that the VPC with the true model has good agreement with the observations.
Slide 49	 Total Dropouts: **23.4%**; Random: 14%; Adverse: 2.0%; Lack of Effect: 6.8%; Remission: 0.6%	Here is a VPC from a large study of patients in an anti-depressant drug trial. The predicted median and 90% PIs do not agree well with the observed values. This is because there are patients who drop out and the pattern of dropout is influenced by the treatment and patient response. This is known as informative missingness.

Slide 50		When it is possible to predict missing values from the data e.g. patients whose HAMD score remains high may dropout because they are not getting better, then this is known as missing at random. A model for the dropout process can be constructed by combining the model predictions for HAMD with a time to event analysis. When the VPC is performed using the dropout model to include a realistic pattern of dropout then the VPC predictions match more closely with the observations. The previous VPC is probably makng good predictions if patients continue with treatment. In that case the observations are 'wrong' because they has been censored by dropouts.
Slide 51		
Slide 52		

Slide 53	Monolix 3.2 Turnover PKPDLIB  ©NHG Holford 2015, all rights reserved.	
Slide 54	Monolix 3.2 Turnover MLX-TRAN CMT  CMT =S0,Imax,C50,kout CMTlib=Rin,Imax,C50,kout MLX-TRAN CMTlib  PKPD Library