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The Impact of Missing Data on Model Evaluation

Marc R. Gastonguay
marcg@metrumrg.com

Metrum Research Group LLC

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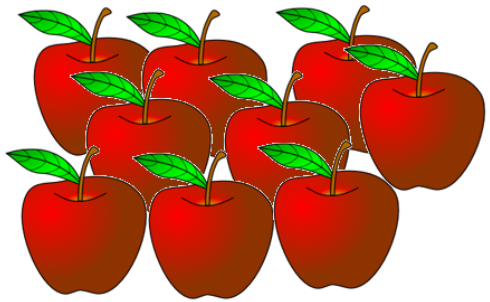
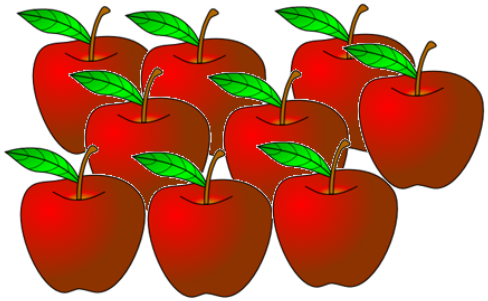
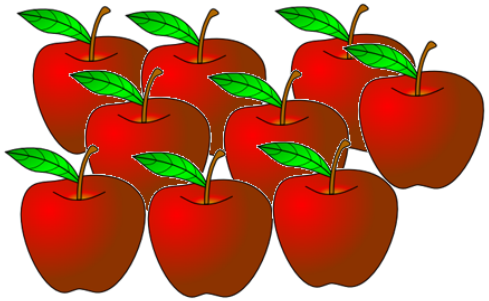
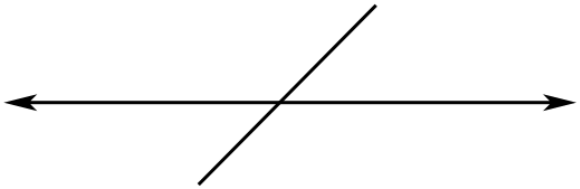
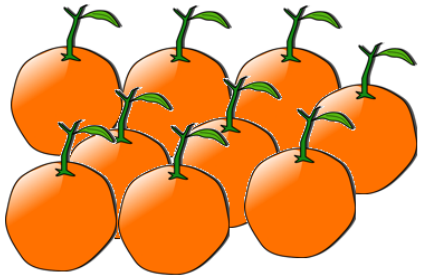
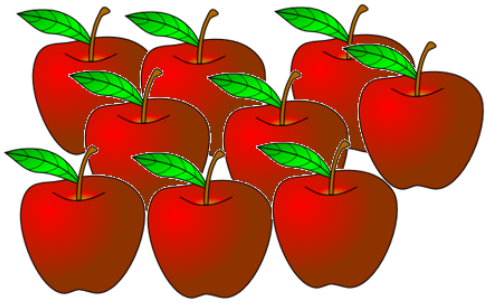


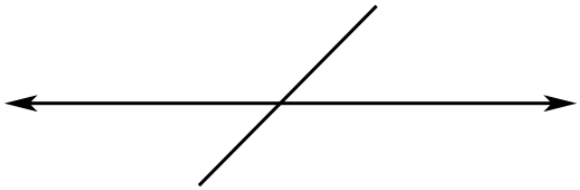


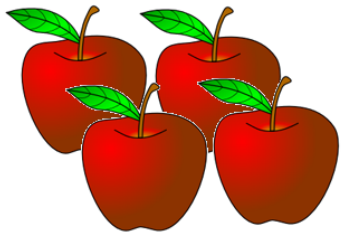












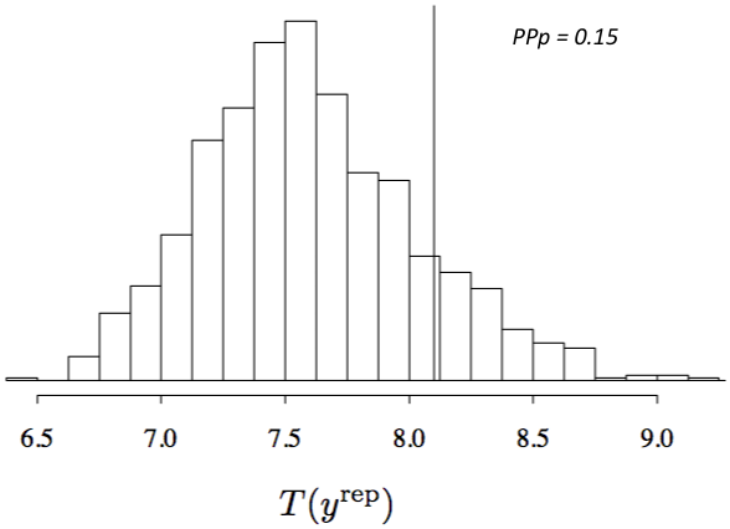
Simulation-Based Model Evaluation Methods

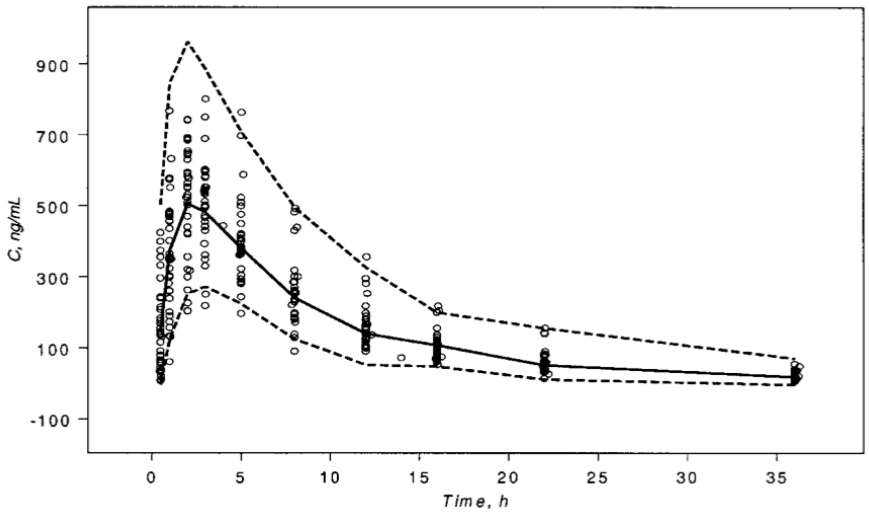
- Posterior Predictive Check

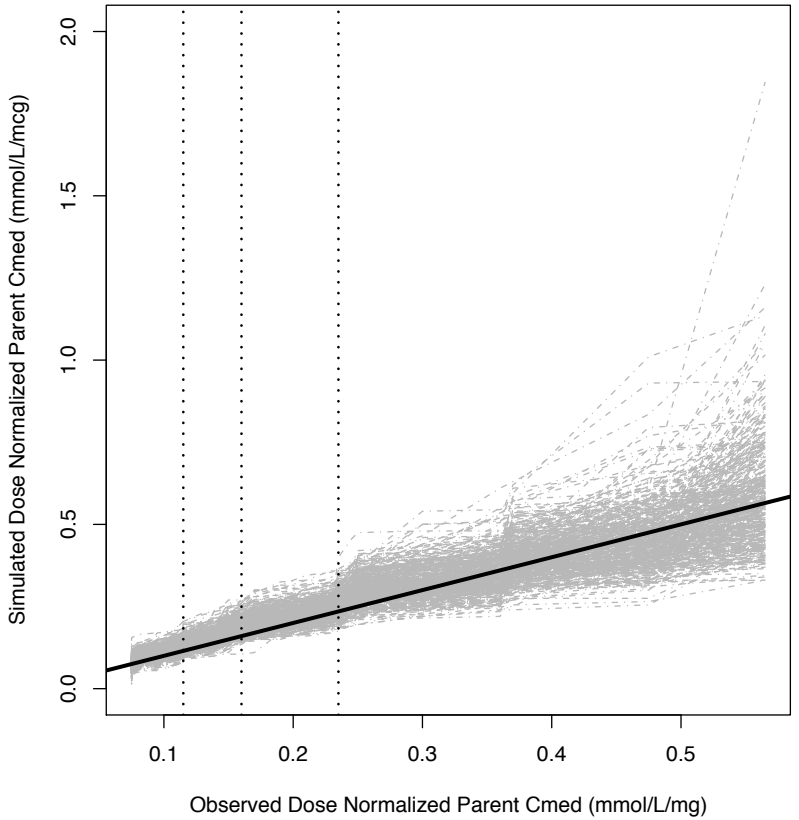
  Gelman, A., Carlin, J. B., Stern, H. S. and Rubin, D. B. (1995). Bayesian Data Analysis. Chapman and Hall, New York.

- Visual Predictive Check (VPC)
- Standardized VPC
- Quantified VPC
- Bootstrap VPC
- Prediction Corrected VPC
- Numeric Predictive Check
- Normalized Prediction Distribution Errors

Some Examples







Clockwise: Gelman, A., Meng, X. L., and Stern, H. S. (1996). Posterior predictive assessment of model fitness via realized discrepancies (with discussion). Statistica Sinica 6, 733-807. Knebel W. & Gastonguay M.R. Predictive Check Q-Q Plot, unpublished results. Shi, J., Ludden, T. M., Melikian, A. P., Gastonguay, M. R. and Hinderling, P. H. (2001). Population pharmacokinetics and pharmacodynamics of sotalol in pediatric patients with supraventricular or ventricular tachyarrhythmia. Journal of Pharmacokinetics and Pharmacodynamics, 28, 555-575.

Impact of Missing Data Mechanism

- **MCAR:** Inference, Model Evaluation, Clinical Trial Simulations - all unaffected by MD
- **MAR:** Inference (typically unaffected), Model Evaluation (affected by MD), Clinical Trial Simulations (affected by MD)
- **NMAR:** Inference, Model Evaluation, Clinical Trial Simulations - all potentially affected by MD.
  Assumptions cannot be evaluated with data at hand.

Is MCAR Assumption Realistic?

- MCAR is not a likely MDM for most longitudinal PKPD data sets
- Diagnostic plots can be helpful to explore possible MDM
  - View MD patterns grouped by independent variables (e.g. Dose, Treatment, Covariates, etc.)
  - View MD patterns by response
- Lack of trend in diagnostics is not a guarantee of MCAR

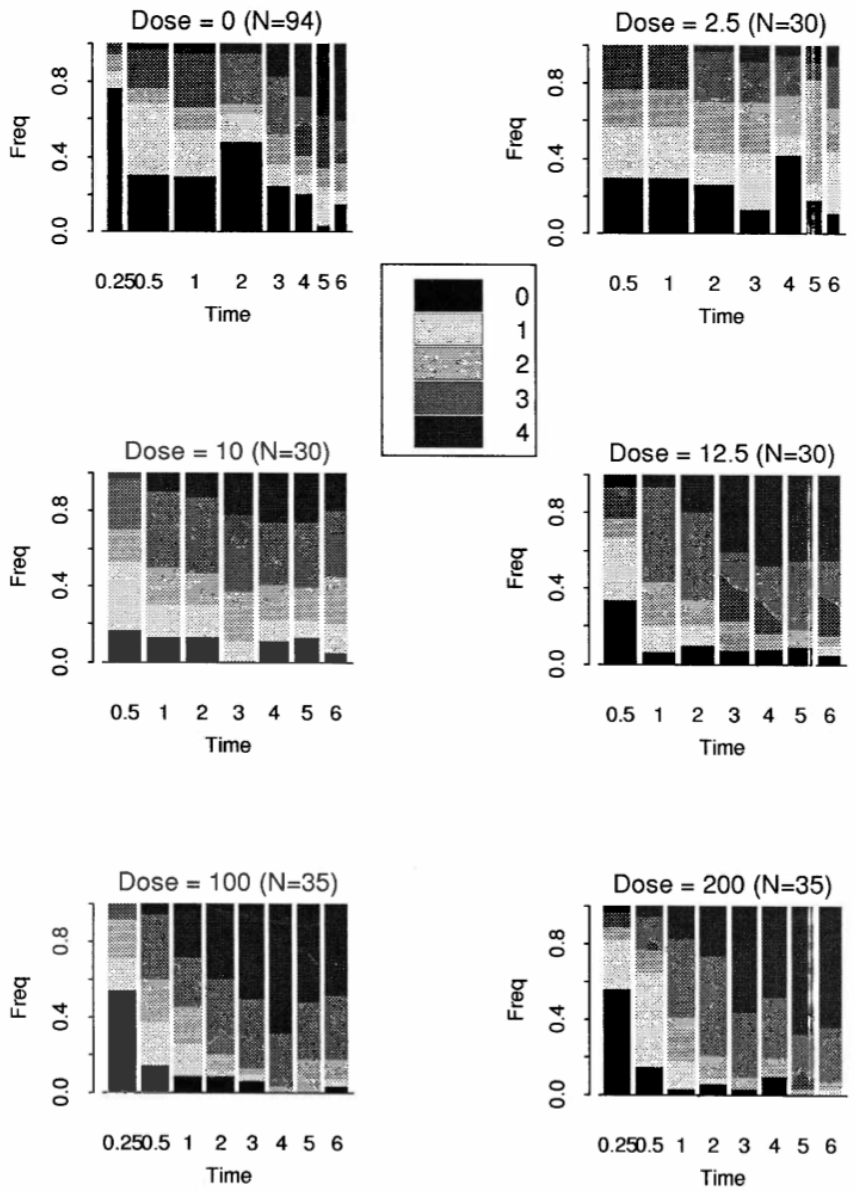
Missing Data Pattern as a Function of Dose and Time

Analysis of Nonrandomly Censored Ordered Categorical Longitudinal Data from Analgesic Trials

Lewis B. SHEINER, Stuart L. BEAL, and Adrian DUNNE

Journal of the American Statistical Association
December 1997, Vol. 92, No. 440, Applications and Case Studies

- Drop-out due to rescue med in acute pain trial
- Column width indicates number of subjects at each time point
- Imbalance in drop-out across doses and over time
- MDM ?

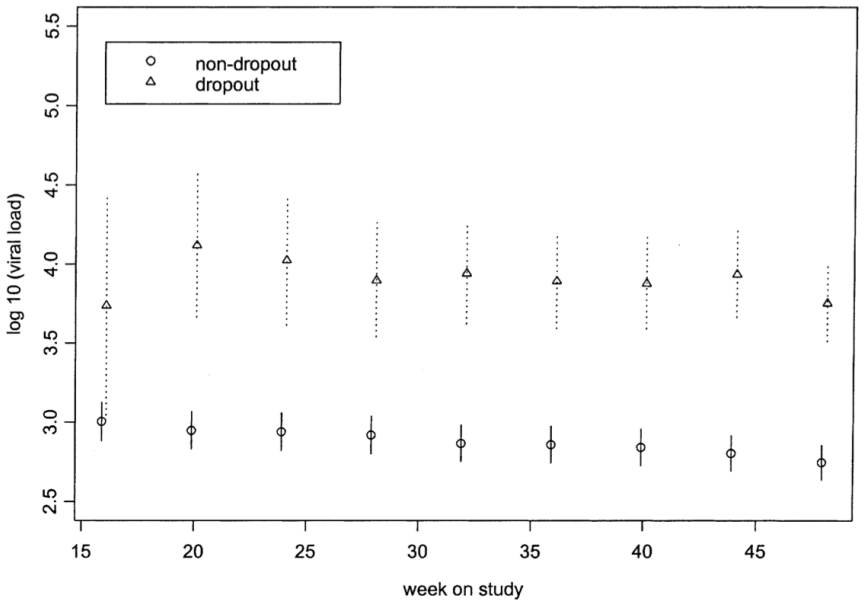


Missing Data Pattern as a Function of Response

A Joint Model for Nonlinear Longitudinal Data with Informative Dropout

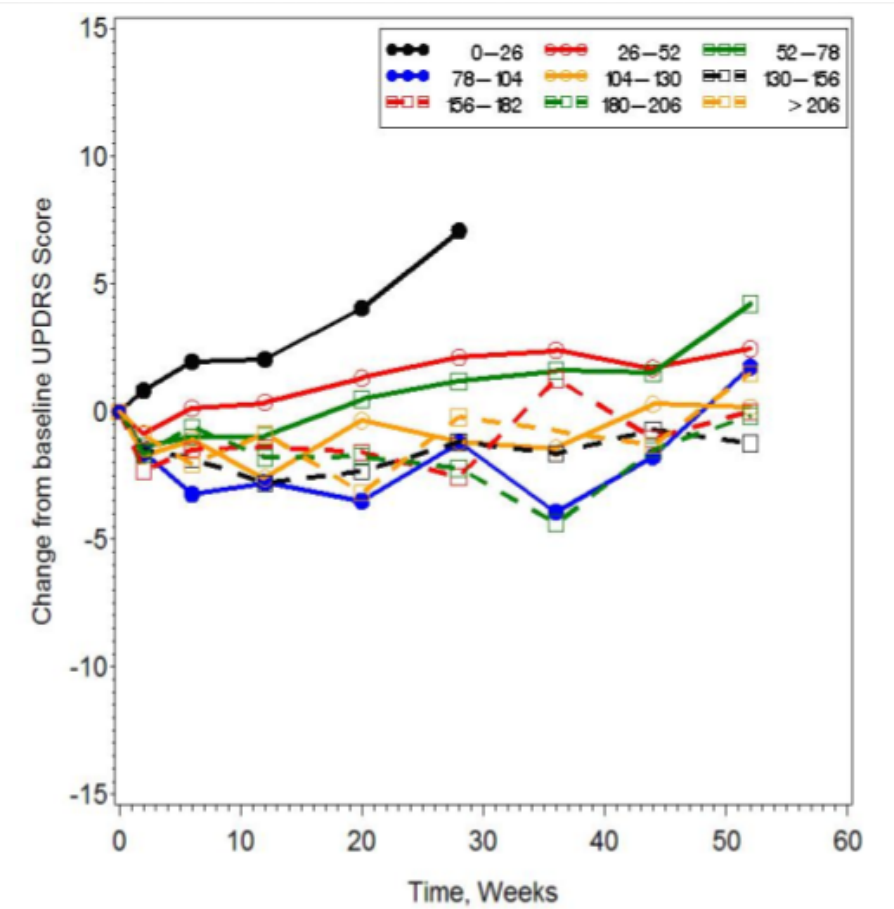
Chuanpu Hu[1,2] and Mark E. Sale[1]

Journal of Pharmacokinetics and Pharmacodynamics, Vol. 30, No. 1, February 2003 (© 2003)



- Viral load response viewed over time by drop-out status
- Triangles represent response for subjects who will drop-out at next visit
- Circles represent response for subjects who will not drop-out at next visit
- Obvious difference in viral load between groups
- MDM appears to depend on Yobs

Response vs. Time by Time to Drop-Out



Bhattaram VA, Siddiqui O, Kapcala L. Learning from Prior Parkinson's Disease Clinical Trials. AAPS Workshop on Demonstrating Disease-modifying Effects for the Treatment of Parkinson's Disease: Drug Development and Regulatory Issues April 28 - 29, 2008 Hyatt Regency Crystal City Arlington, VA http://www.aapspharmaceutica.com/meetings/files/119/Bhattaram.pdf

- Placebo group Parkinson's Disease progression, measured by UPDRS Score
- Positive change indicates worsening of disease
- Colored lines indicate subjects binned by time to drop-out
- Individuals with earlier drop-out (e.g. black line: duration 0-26 weeks) also exhibit increased rate of disease progression.
- MDM appears to depend on Yobs

Factors to Consider for Simulation-Based Model Evaluation

- **Design for Simulation Replicates:** Use planned complete data design
- **Simulations:** Hierarchical MEM with/without model for MDM
- **Observations:** Observed cases only, or imputation to create complete data set

Simulate Using Planned Complete Data Design

Observed Cases Only

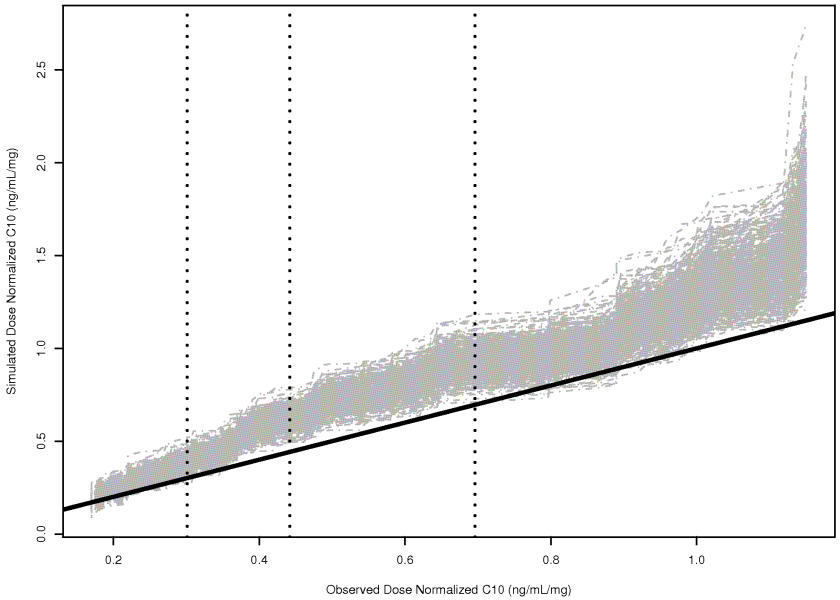
ID	TIME	DV	MDV	R
1	0	23	0	1
1	10	18	0	1
1	24	19	0	1
2	0	25	0	1
2	10	10	0	1

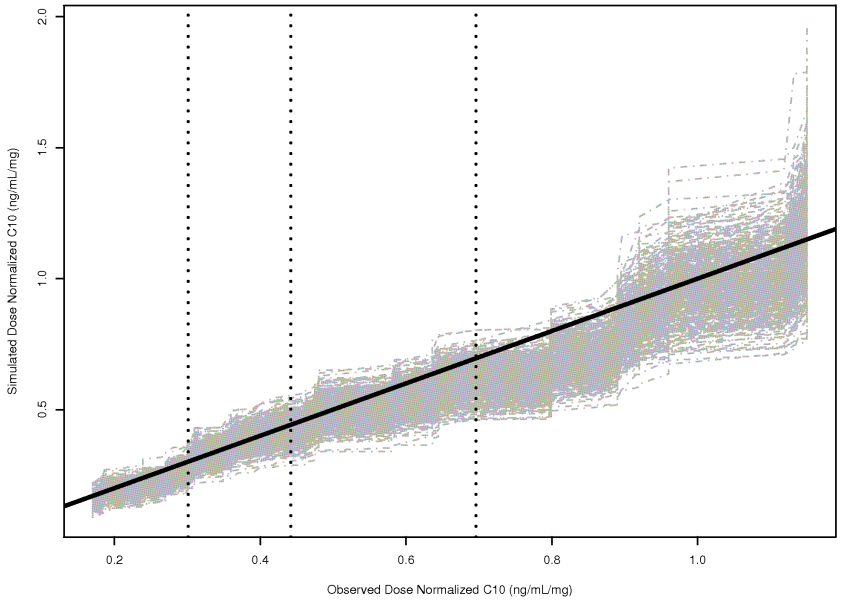
Planned Complete Data Design

ID	TIME	DV	MDV	R
1	0	23	0	1
1	10	18	0	1
1	24	19	0	1
1	48	.	1	0
2	0	25	0	1
2	10	10	0	1
2	24	.	1	0
2	48	.	1	0

- Simulations using observed cases only as design template may result in misleading model evaluation results.

BQL Censored: Simulate Using Planned Complete Data Design





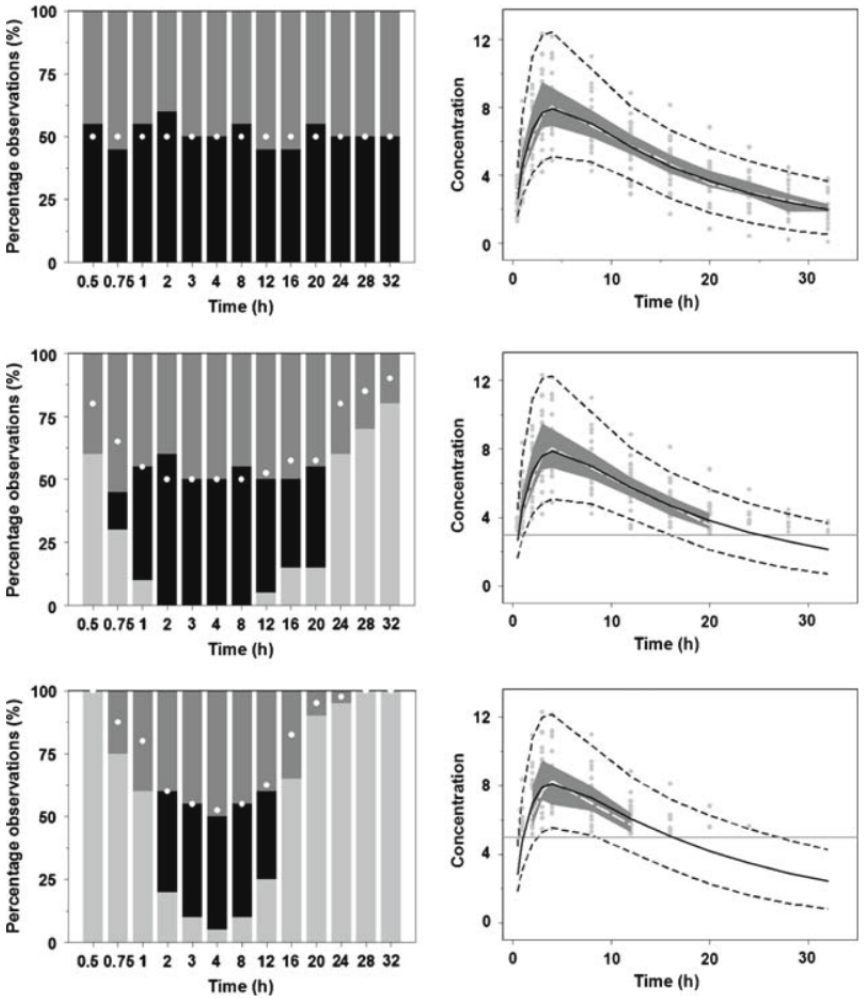
- Predictive check Q-Q Plot for the same population PK model under observed cases design (left) or planned complete data design (right). Simulated data BQL were censored in each case.
- Simulation from observed cases design results in excessive censoring of simulated data

Restrict Check to Regions w/ Minimal Missing Data

J Pharmacokinet Pharmacodyn (2008) 35:185–202
DOI 10.1007/s10928-007-9081-1

Extensions to the Visual Predictive Check to facilitate model performance evaluation

Teun M. Post · Jan I. Freijer · Bart A. Ploeger · Meindert Danhof



- Bar-plot quantifies fraction of missing data, as well as fraction above or below median simulated value
- Missing Data indicated by light gray bars
- Difficult to assess model performance in regions where fraction of missing data is large

Imputation for Complete "Observed" Data Set

- Create complete data set by imputing values where data are missing

Planned Complete Data Design With Imputation				
ID	TIME	DV	MDV	R
1	0	23	0	1
1	10	18	0	1
1	24	19	0	1
1	48	16	1	0
2	0	25	0	1
2	10	10	0	1
2	24	8	1	0
2	48	6	1	0

- Single Imputation
  - LOCF
  - BOCF
  - Conditional Model Prediction: conditional on estimated individual random effects, given observed data
- Multiple Imputation
  - Model Simulated: Monte Carlo simulation at missing data time-points from population mean/variance model derived from observed data
  - Other random sampling strategies

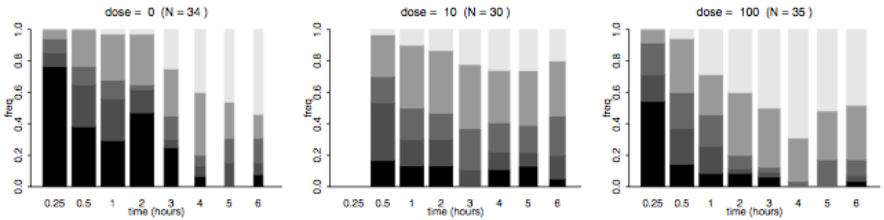
Single Imputation with BOCF

Biometrics 61, 74–85
March 2005

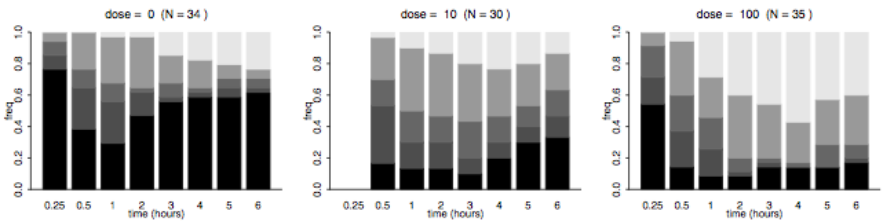
Multiple Imputation for Model Checking: Completed-Data Plots with Missing and Latent Data

Andrew Gelman,[1,*] Iven Van Mechelen,[2] Geert Verbeke,[3]
Daniel F. Heitjan,[4] and Michel Meulders[2]

Observed data display

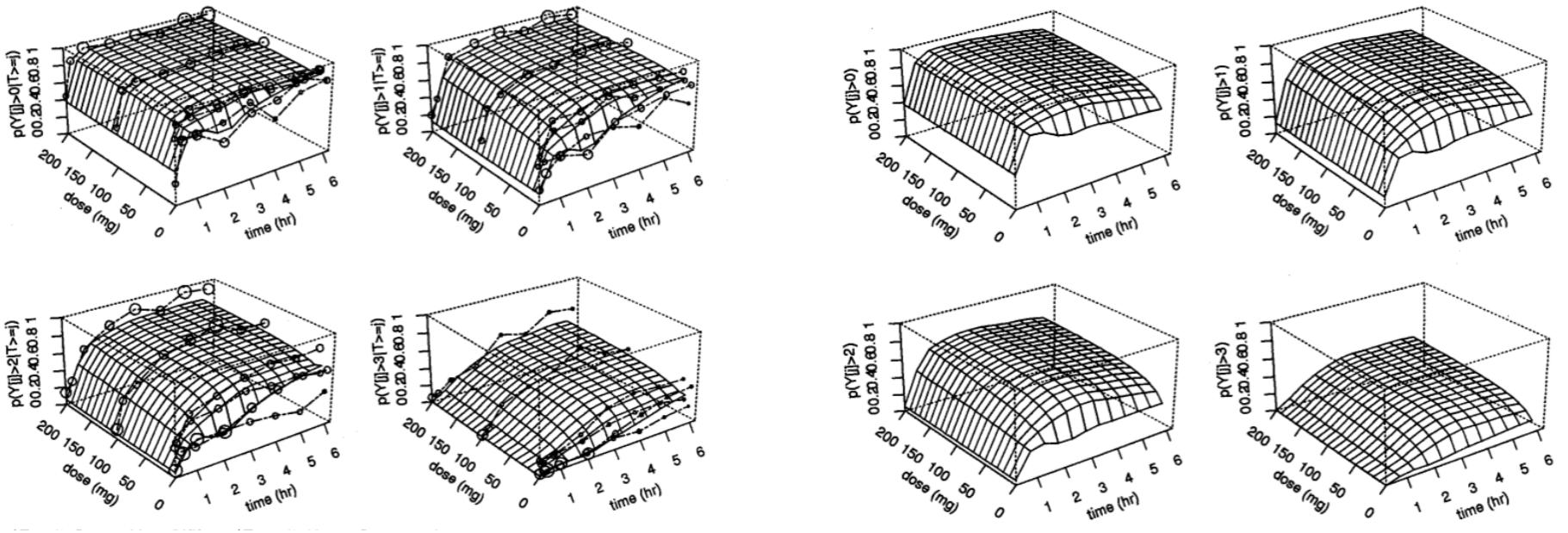


Completed data display



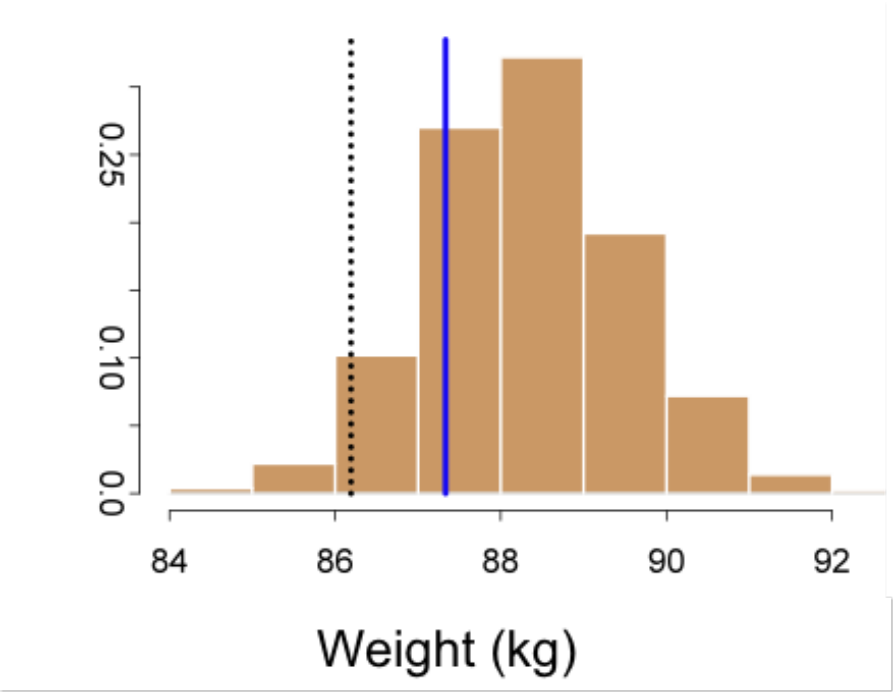
- Same data set as Sheiner et al (1997) diagnostic plot shown earlier
- Added complete data display (bottom) by single imputation with BOCF
- This complete data display could be compared with complete data simulations from NLME PKPD model (results not shown)

Single Imputation with Conditional Model Prediction



- Also from Sheiner et al (1997). Response surface based on observed cases (left) or imputed complete data (right).
- Inferences from complete data under conditional model estimates are more meaningful
- Could also be compared to complete-data simulation (not shown)

Single Imputation with Conditional Model Prediction



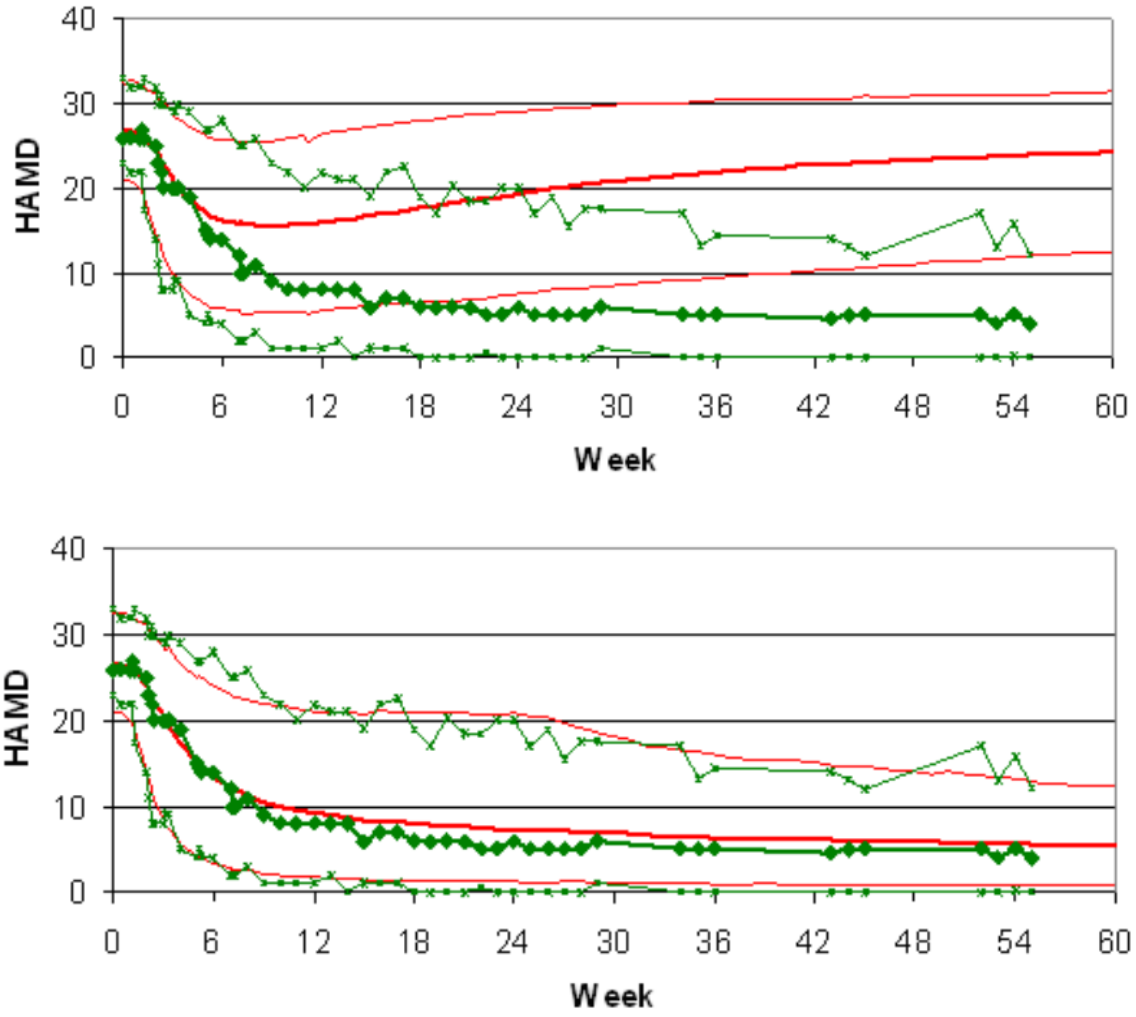
- Solid blue line is observed after imputation (PPp = 0.72)
- Dotted line is observed without imputation (PPp = 0.91)

- Predictive check for a longitudinal population PD mixed-effects model
- Mean weight at 6 months is endpoint
- Greater than 36% drop-out in this treatment group
- Missing data imputation with conditional PD mixed-effects model prediction
- Imputation allows for more accurate model assessment

Simulations with Joint Response and MDM Model

- Develop models for response and for MDM, given observed data
- Compare response endpoint in observed cases with simulated responses, adjusted with MDM model
- Conduct a separate predictive check to assess performance of model describing the MD pattern (e.g. longitudinal fraction of missing data)

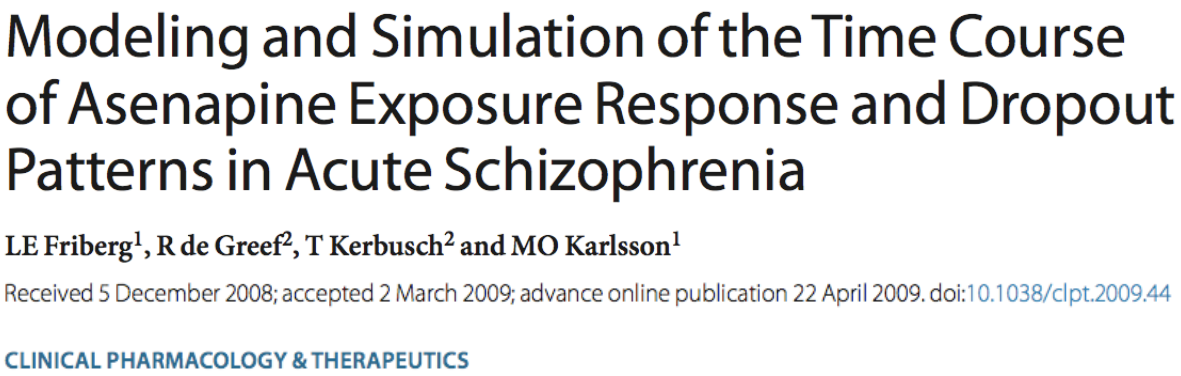
Modeling Longitudinal Depression Trial



A Tutorial on Visual Predictive Checks. Nick Holford, Mats Karlsson. PAGE 17 (2008) Abstr 1434 [www.page-meeting.org/?abstract=1434] (originally presented at the Lewis Sheiner Memorial Symposium in 2006).

- Top: VPC for complete data simulation quantiles under NLMEM (red), compared to observed quantiles (green)
- Bottom: VPC for same response model, adjusted by time-to-event drop-out model

Modeling Longitudinal Schizophrenia Trial



Modeling and Simulation of the Time Course of Asenapine Exposure Response and Dropout Patterns in Acute Schizophrenia

LE Friberg[1], R de Greef[2], T Kerbusch[2] and MO Karlsson[1]

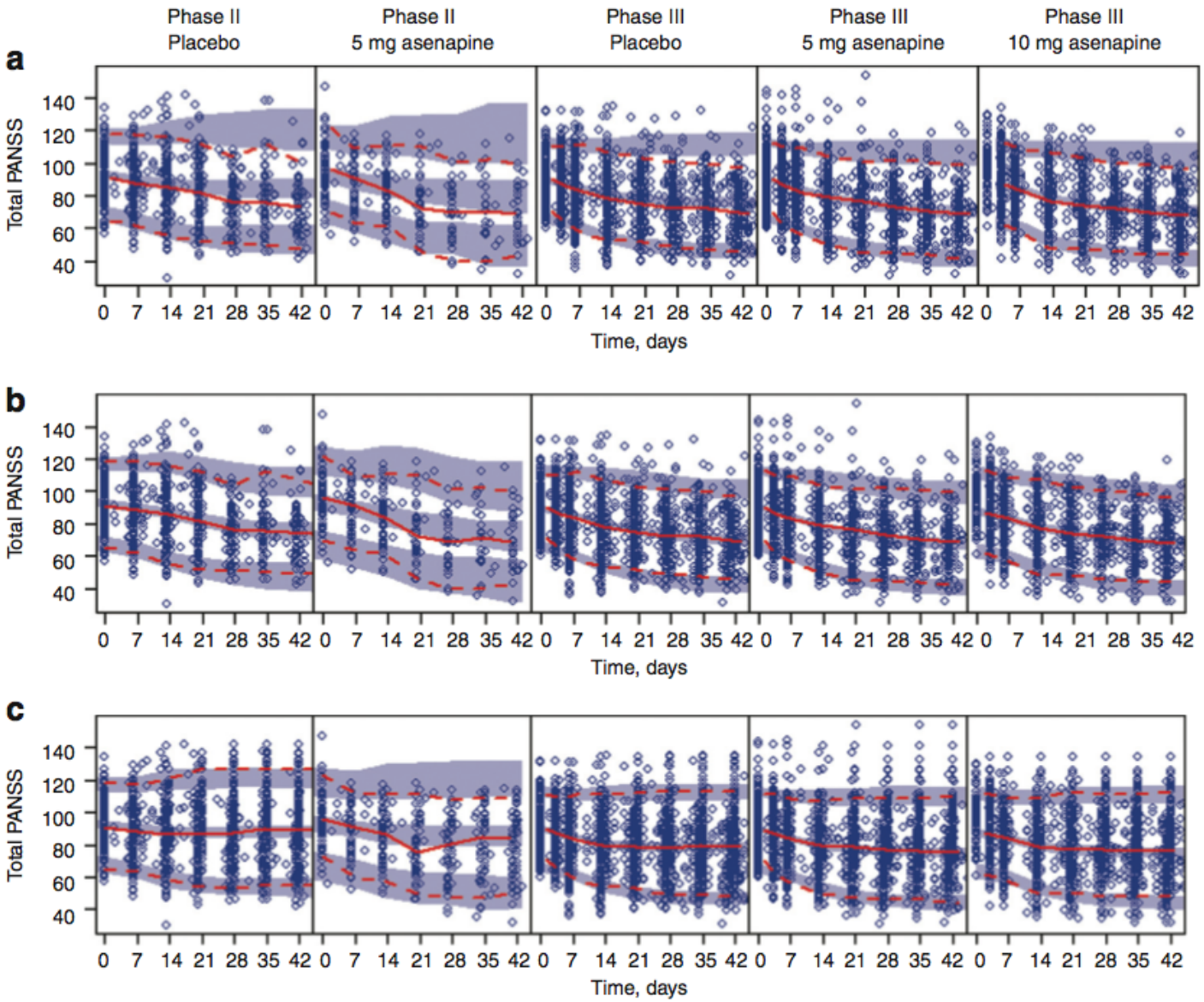
Received 5 December 2008; accepted 2 March 2009; advance online publication 22 April 2009. doi:10.1038/clpt.2009.44

CLINICAL PHARMACOLOGY & THERAPEUTICS

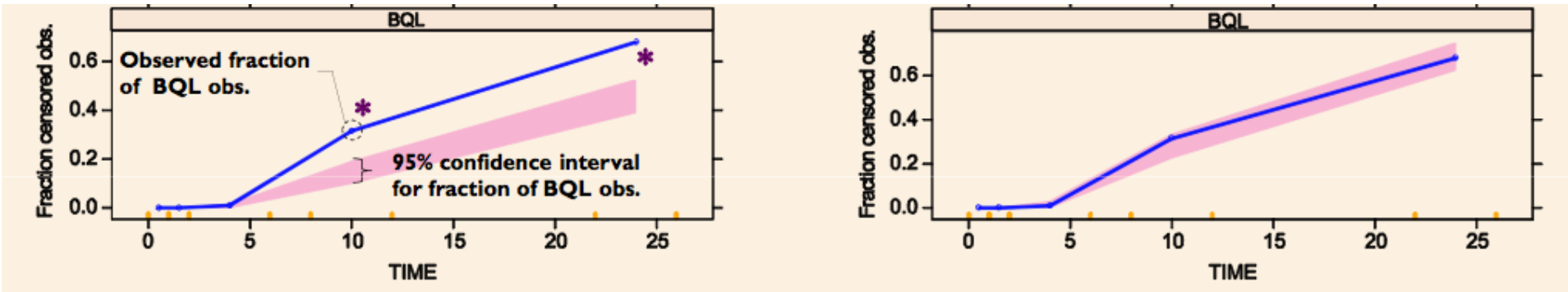
- Developed models for both PANSS-total response and MDM (logistic models for probability of drop-out at each visit interval)

- VPC comparisons
  a. Observed cases, with simulations under the NLME PANSS response model
  b. Observed cases with simulations under NLME PANSS response model adjusted by MDM model
  c. Observed complete data under LOCF imputation, with simulated complete data using combined response/MDM model and LOCF imputation

Modeling Longitudinal Schizophrenia Trial

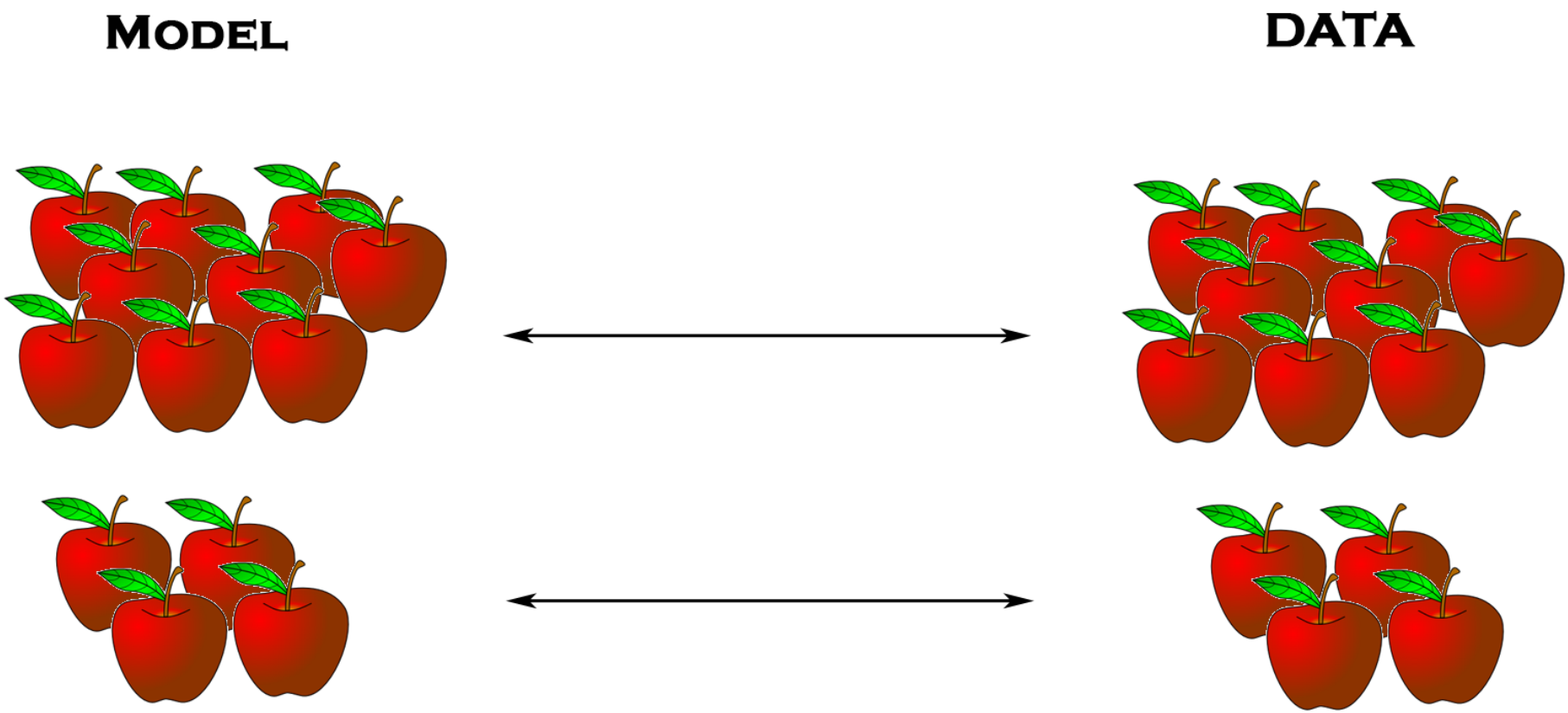


Check Performance of MDM Model



Visual Predictive Checks for Censored and Categorical data. Martin Bergstrand, Andrew C. Hooker, Mats O KarlssonPAGE 18 (2009) Abstr 1604. [www.page-meeting.org/?abstract=1604]

- Comparison of two population PK models
- Left: No Likelihood adjustment and BQL data excluded, Right: BQL data treated as censored observations.
- View performance of model for MD pattern (e.g. fraction of MD over time)


MODEL
DATA

Key Points

- Simulate under planned complete data design.
- Use single/multiple imputation to create complete data set
  - Compare complete observed data with complete simulated data
- Simulate with joint response and MDM model
  - Compare response in observed cases with response in MDM model-adjusted simulated data
  - Compare observed missing data pattern with simulated missing data pattern
- Run multiple simulation-based diagnostics for multiple model/data features, with an eye on the intended use of the model.

Warning

- There is no model checking method that can rule-out the possibility of a NMAR mechanism
- One useful activity is to perform sensitivity analysis to explore impact of NMAR mechanism (Dan Heitjan)

Acknowledgements

- Jonathan French
- Joe Hebert
- Dan Heitjan
- Nick Holford
- Bill Knebel
- Patanjali Ravva
- Jim Rogers
- Jun Shi

Related Poster Presentations at ACOP 2009: Model Checking

- Prediction Corrected Visual Predictive Checks. Martin Bergstrand, Andrew C. Hooker, Johan E. Wallin, Mats O. Karlsson.
  F7, Mon. PM
- Informativeness of Internal and External Validation Techniques in Various Simulation Settings and Across Algorithms. Paul G Baverel, Kristin E Karlsson, Mats O Karlsson
  V7, Mon. PM
- Evaluation of different tests based on observations for external model evaluation of population analyses. France Mentre, Karl Brendel, Emmanuelle Comets
  M7, Mon. PM

Related Poster Presentation at ACOP 2009: Modeling MDM

- Modeling Pain Memory is Central to Characterizing the Hazard of Dropping Out in Acute Pain Studies. Paul M. Diderichsen, Sandeep Dutta, Wei Liu, Peter A. Noertersheuser, Walid Awni
  P8, Weds. AM
- Optimal design on Time-To-Event models with an emphasis on dropouts in Disease Progression studies. Joakim Nyberg, Anna Svensson, Mats O. Karlsson, Andrew C. Hooker
  P5, Weds. PM
- Comparisons of modeling dropout as Time-to-Event data or Binary data using logistic regression. Klas J F Petersson, An M Vermeulen, Lena E Friberg
  H4, Tues. PM