Informative Dropout and Visual Predictive Check of Exposure-Response Modeling of Ordered Categorical Data

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PAGE 2011

Overview

- Recently appeared in J/PK/PD (2011) 38: 237-290
  - Dropout classification, informative dropout modeling
  - Conditional visual predictive check (VPC)
    - Statistically appropriate
    - Independent on correlated factors, e.g., future dosing
    - Same principle applies to checking dropout model
  - Semi-mechanistic PK/PD driven logistic regression model
    - Investigation of tolerance
  - Model validation
    - Using data from separate study is practically the only valid approach
    - Avoid subjective motivations to bias the results toward calling model "validated," e.g., using posthoc estimates, which may mean using validation data twice
    - VPC likely the best tool, at least for longitudinal data

Informative Dropout Illustration
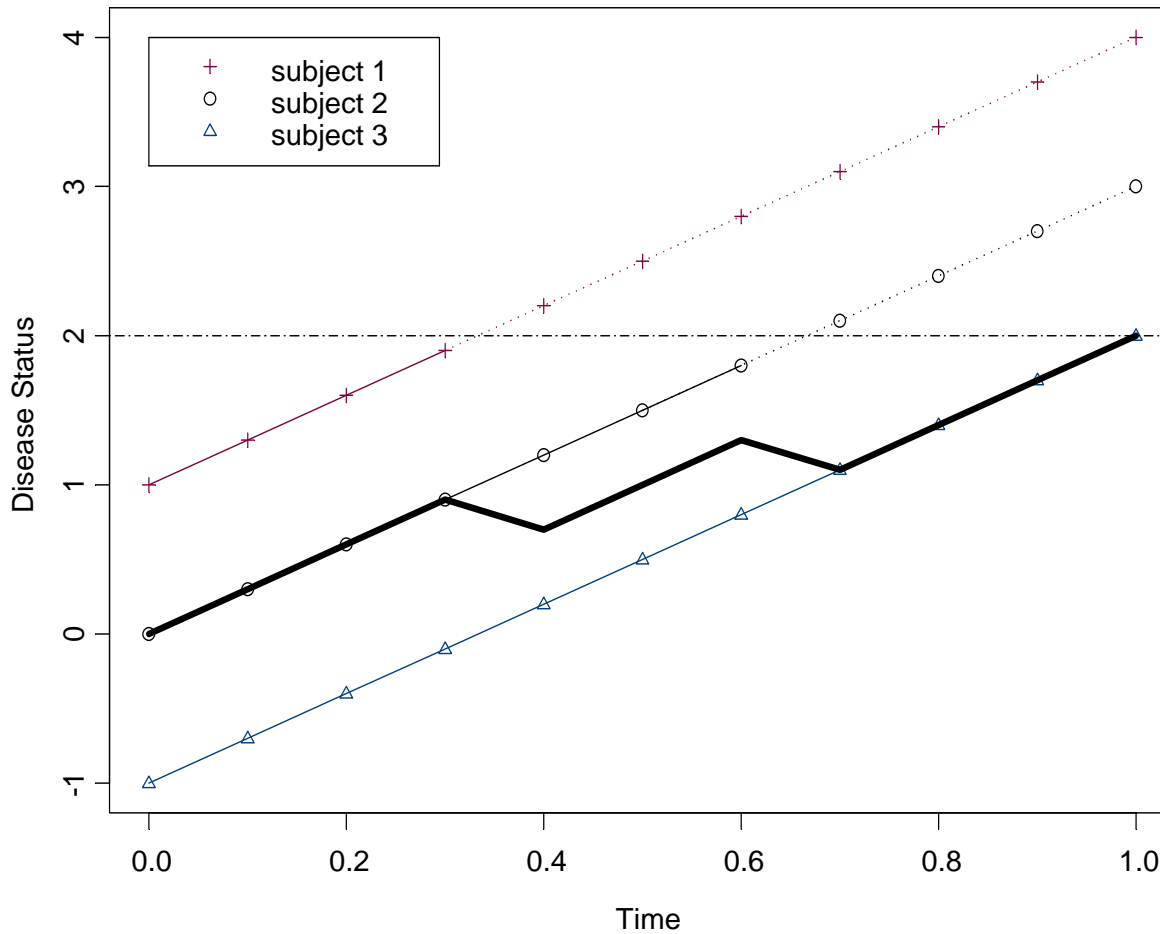
Dropout Classification and Modeling

- Notation
  - T: dropout time
  - Yobs = $(Y1, Y2, \ldots, Yi)$: observed response for a subject
  - Ymis = $Y(t)$: unobserved true response during time interval (ti, T)

- Completely random dropout (CRD), if
  - T is independent of (Yobs, Ymis)
    - Can ignore dropout

- Random dropout (RD), if
  - T depends on Yobs, but not Ymis
    - Can ignore dropout in modeling

- Informative dropout (ID), if
  - T depends on Ymis
    - Must model dropout jointly with response

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Informative Dropout Modeling
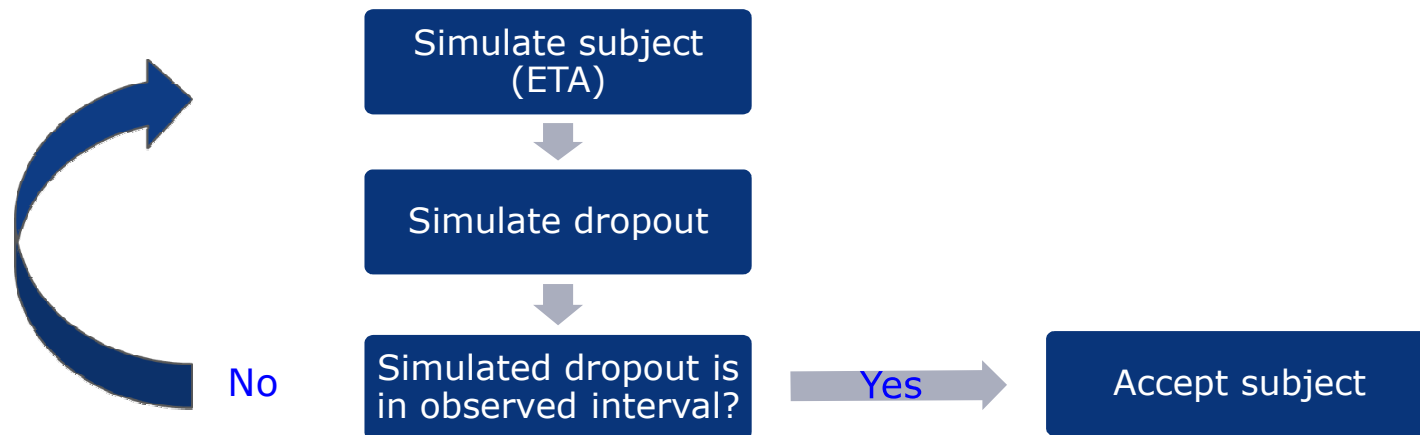
- Jointly model response data and dropout – 2 ways to factorize (specify) likelihood

  - $P(Yobs, T \mid \varphi, \theta) = P(Yobs \mid \theta) * P(T \mid Yobs, Ymis, \varphi)$

    - (Selection model) Specify response model, and how dropout depends on response

      - Good for PK/PD modeling

  - $P(Yobs, T \mid \varphi, \theta) = P(T \mid \varphi) * P(Yobs \mid \theta, T)$

    - (Pattern mixture) Specify dropout model, and how response depends on dropout

      - Motivation for conditional VPC

- Directly implementable in NONMEM

Ordinary VPC of Longitudinal Data

- Simulate joint distribution P(Y, T) of longitudinal data AND dropout, then ignore dropout

  - Observed data to be compared with is actually (Y|T), longitudinal data given dropout

  - Fine if Y, T are independent, but not under informative dropout

- Additional problem: simulated dropout for a subject may occur after actual dropout

  - Requires the assumption that future dosing is known with certainty

    - Problem with most clinical trial conduct, especially if titration is present

    - Additional uncertainty and potential bias

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Conditional VPC of Longitudinal Data

- Statistically appropriate approach: generate P(Y | T), the distribution of longitudinal data conditional on (observed) dropout

- Repeated simulation of each subject until simulated dropout falls in observed dropout time interval

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        ┌─────────────────────┐
        │  Simulate subject   │
        │       (ETA)         │
        └─────────────────────┘
                  ↓
        ┌─────────────────────┐
        │  Simulate dropout   │
        └─────────────────────┘
                  ↓
  No    ┌─────────────────────┐   Yes    ┌─────────────────┐
 ←──────│ Simulated dropout is│ ───────→ │ Accept subject  │
        │ in observed interval?│          └─────────────────┘
        └─────────────────────┘
```

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Checking Dropout Model

- Conditional approach more appropriate, similar to checking longitudinal data

- Conditioning on longitudinal instead of dropout
  - Calculate posthoc ETAs from longitudinal data, then put in individual dropout model
    - Calculation would be more accurate if also using dropout, however would amount to using dropout data twice

- Model checking/validation: use modified Cox-Snell residual (straight line if good fits)

Application: Study Design and Data

PGA: 6-point measure of disease severity

- 0=cleared; 1=minimal, … 5=severe
- PGA≤1 and 2 used for regulatory purposes

Study PHOENIX 2 (used for initial model development)

- Week 0 – 12: PBO / 45mg / 90mg / Loading + Q12 weeks
- Week 12 – 28: PBO crossover
- Week 28 – 52: Dose optimization (escalation)
- Week 52 – : long term extension (open label)
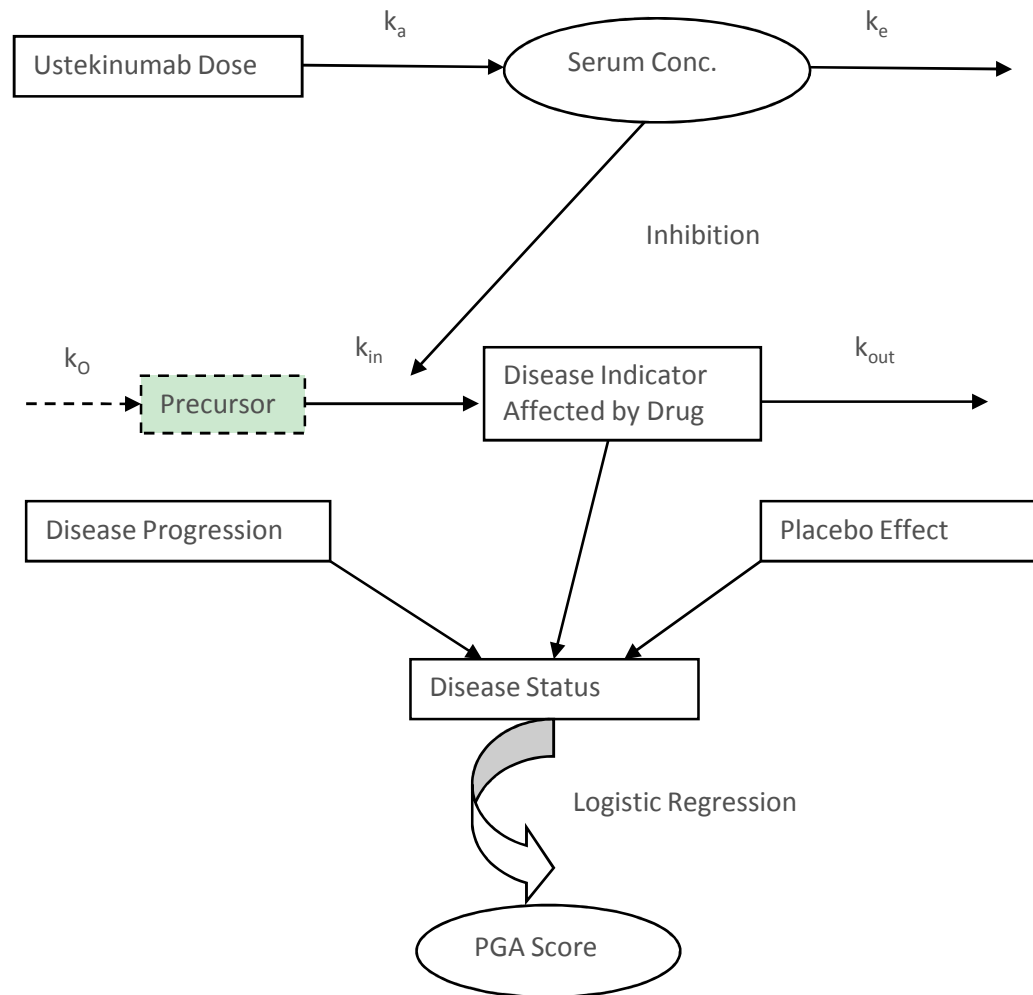- 1,312 subjects, 9,723 PK records, 21,711 PGA scores, 17% dropout

Study PHOENIX 1 (reserved for model validation)

- Similar design but some data up to week 152
- 665 subjects, 9,617 PK records, 19,957 PGA scores, 21% dropout

Checking Whether Complete Random Dropout Is Reasonable
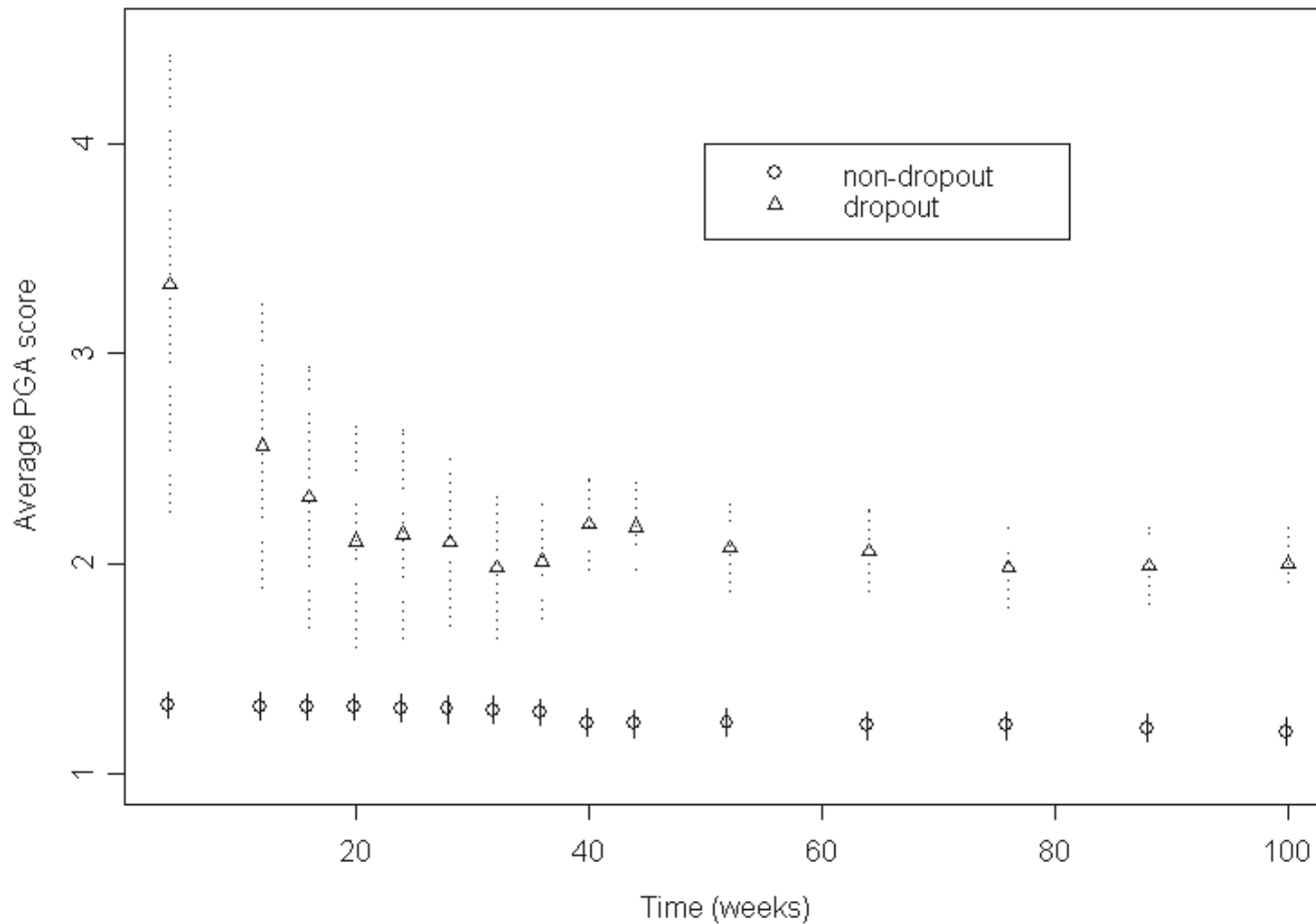
PK/PD Model Overview

Latent Variable Indirect PK/PD Model

- With logit(x) = log[x / (1-x)], model
    - Logit[prob(PGA ≤ k)] = $a_k + f_z(t) + f_p(t) + f_d(t) + \eta$

- Baseline probability: a_k

- Disease progression $f_z(t) = \beta t$

- Placebo effect: $f_p(t) = Plb_{max}[1 - exp(-R_p t)]$

- Drug effect: $f_d(t) = DE[1 - R(t)]$

$$\frac{d\,R(t)}{dt} = k_{in}\left(1 - \frac{C_p}{IC_{50} + C_p}\right) - k_{out}\,R(t)$$

- (Precursor model was not significant after incorporating disease progression)

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(Joint) Dropout Model with Weibull Hazard

Completely random (CRD)

- $h(t) = a\lambda t^{a-1}$
- Independent of observed or unobserved longitudinal data

Random (RD)

- $h(t) = a\lambda t^{a-1} \exp(-\beta_O Y_O)$
- Depend on past observed data Y_O but not on unobserved data

Restrict Informative (RID)

- $h(t) = a\lambda t^{a-1} \exp(-\beta_1 Y_U)$
- Depend on unobserved disease status $Y_U = f_z(t) + f_p(t) + f_d(t) + \eta$

Categorical data less informative; RID likely will fit better than RD
Can graphically assess whether CRD is realistic, but not RD or RID

Modeling Scheme

Initial model using Phoenix 2
- CRD, RD, ID and RID, combined with constant and Weibull hazards
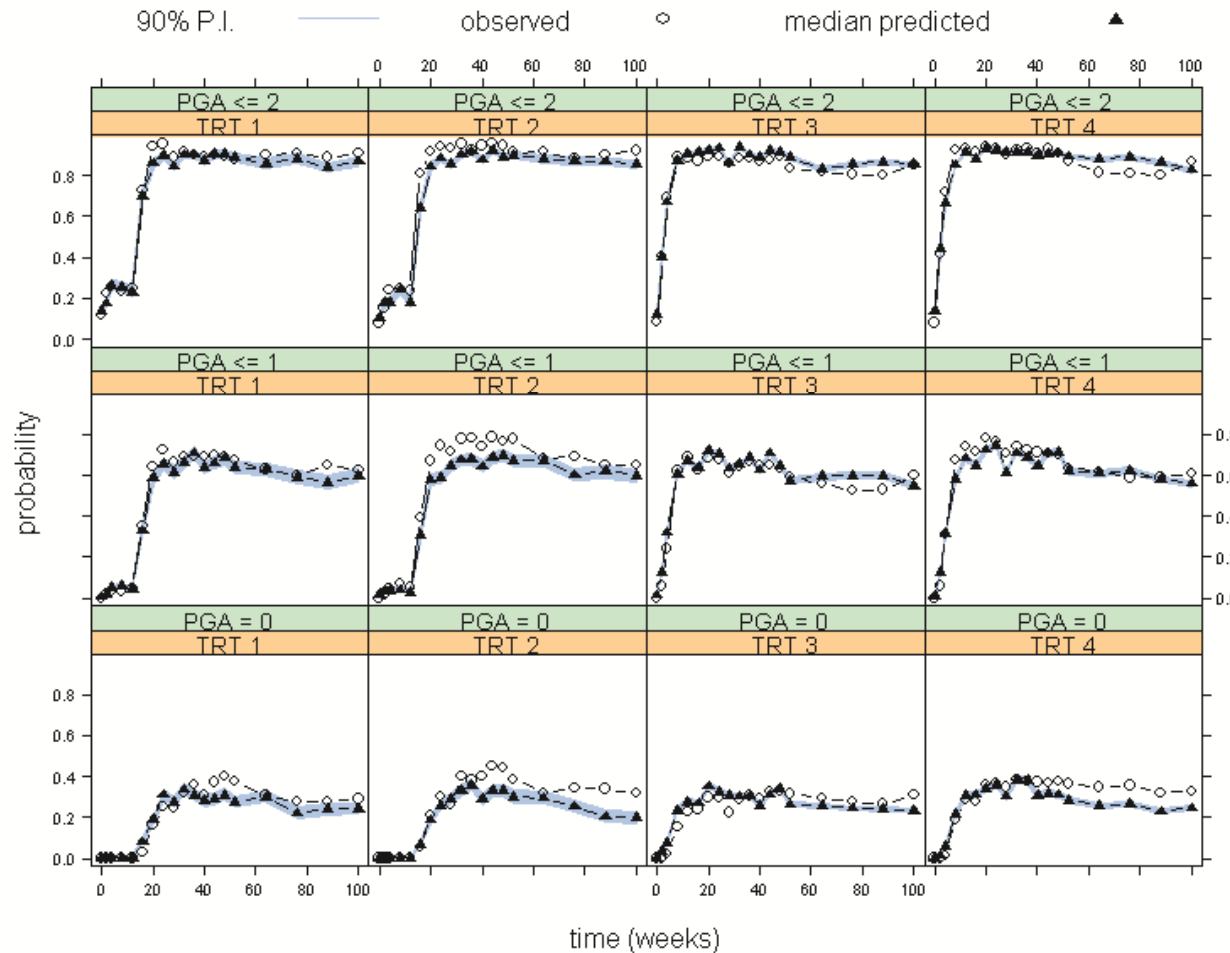- RID with Weibull dropout fits best

(External) validation using Phoenix 1

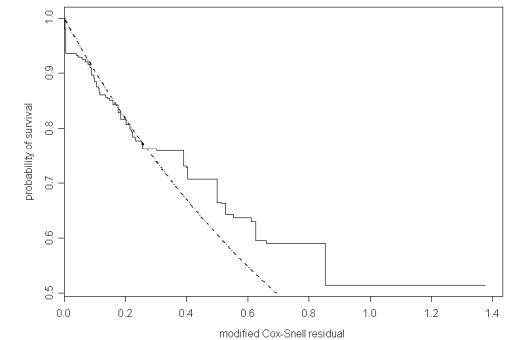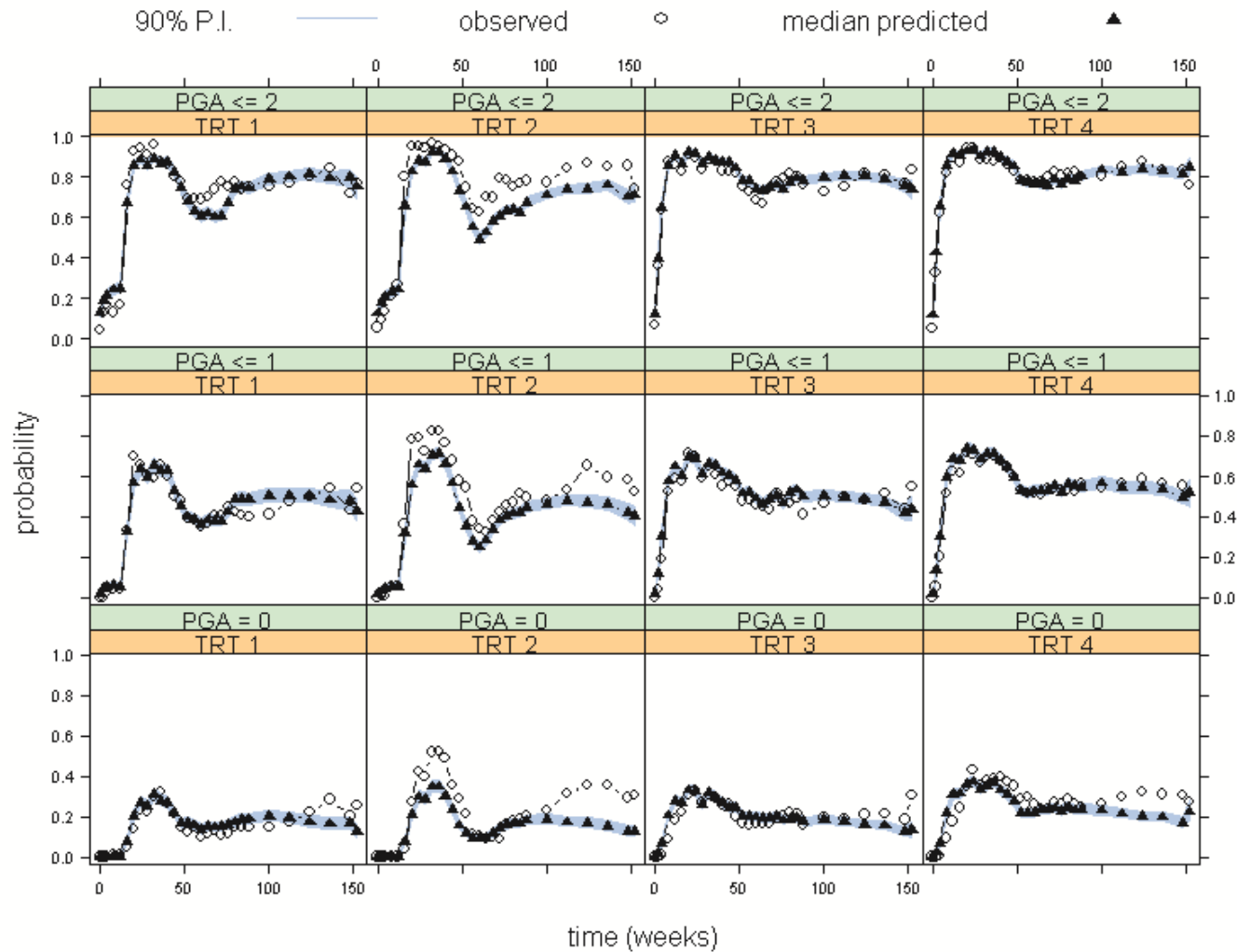**Refit the model combining Phoenix 1 and 2**
- Conditional VPC for response and dropout

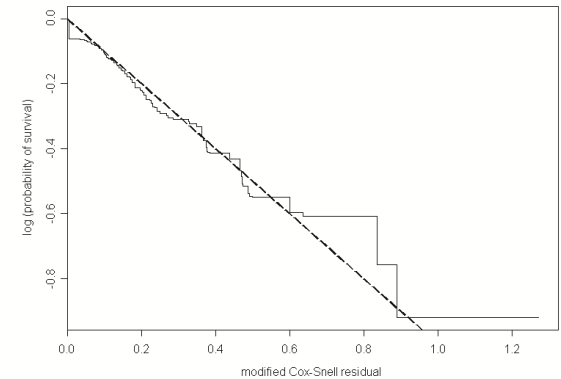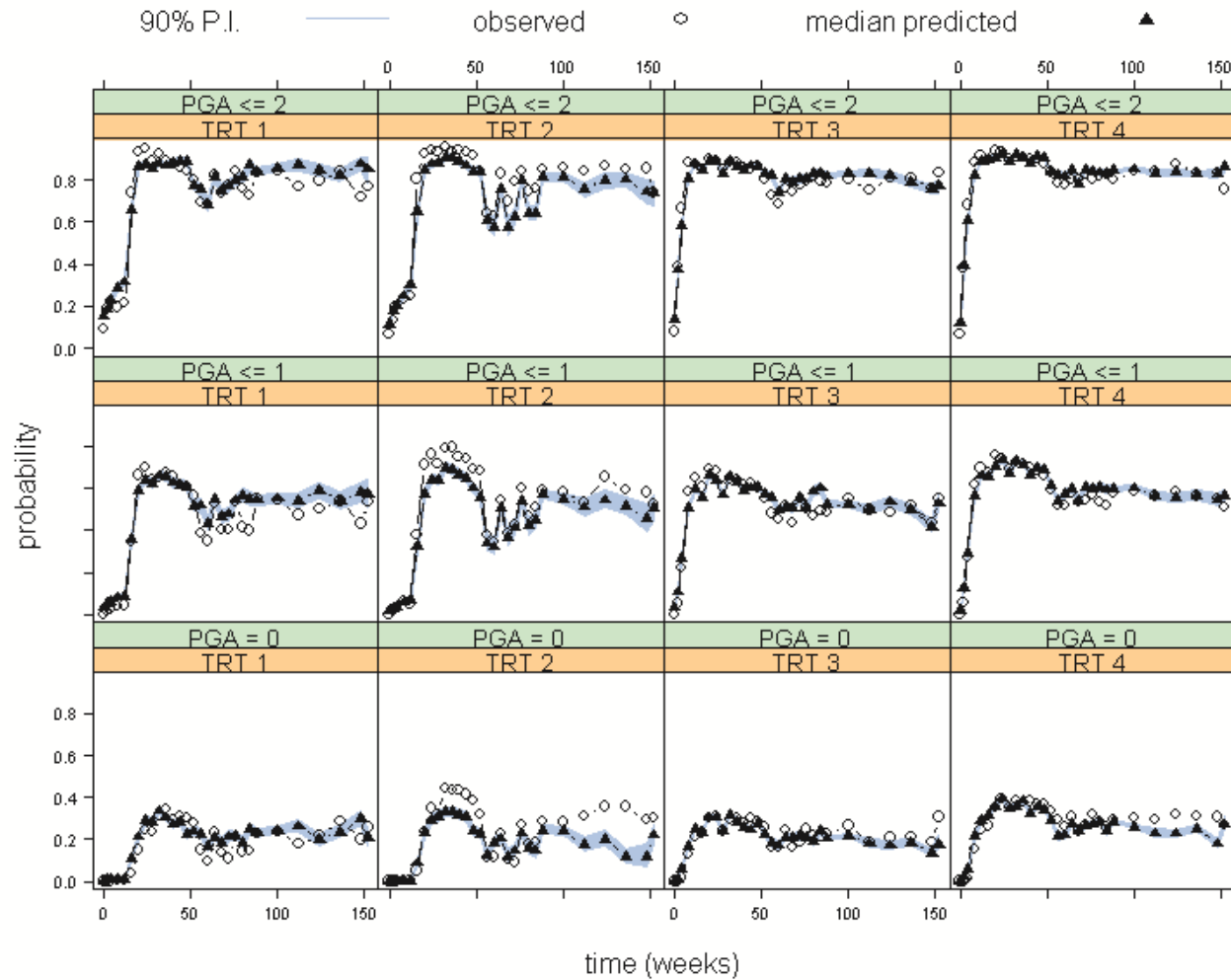**Conditional approach used for VPC and dropout in all 3 stages**

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Initial Model Conditional VPC
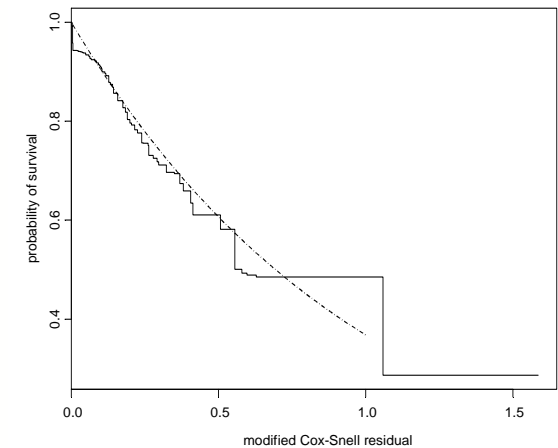
Validation Using Phoenix 2 – Conditional VPC

Final Model with Combined Data

Conclusion

Informative dropout modeling extends straightly to categorical data

- Weibull dropout model can account for time-vary hazards
- RID likely to fit better

Use conditional approach for model checking (VPC)

- Statistically appropriate
- Independent of unknown future dosing: less uncertainty, more accurate