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

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Overview

  - 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
  - $Y_{\text{obs}} = (Y_1, Y_2, \ldots, Y_i)$: observed response for a subject
  - $Y_{\text{mis}} = Y(t)$: unobserved true response during time interval $(t_i, T)$

- **Completely random dropout (CRD), if**
  - $T$ is independent of $(Y_{\text{obs}}, Y_{\text{mis}})$
    - Can ignore dropout

- **Random dropout (RD), if**
  - $T$ depends on $Y_{\text{obs}}$, but not $Y_{\text{mis}}$
    - Can ignore dropout in modeling

- **Informative dropout (ID), if**
  - $T$ depends on $Y_{\text{mis}}$
    - Must model dropout jointly with response
Informative Dropout Modeling

• Jointly model response data and dropout – 2 ways to factorize (specify) likelihood
  
  \[ P(Y_{obs}, T \mid \phi, \theta) = P(Y_{obs} \mid \theta) \times P(T \mid Y_{obs}, Y_{mis}, \phi) \]
  
  • (Selection model) Specify response model, and how dropout depends on response
    
    – Good for PK/PD modeling
  
  \[ P(Y_{obs}, T \mid \phi, \theta) = P(T \mid \phi) \times P(Y_{obs} \mid \theta, T) \]
  
  • (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
Conditional VPC of Longitudinal Data

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

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

Ustekinumab Dose → Serum Conc. → Disease Indicator Affected by Drug → Disease Status → PGA Score

- $k_a$: Absorption rate constant
- $k_e$: Elimination rate constant
- $k_0$: Degradation rate constant
- $k_{in}$: Inhibition rate constant
- $k_{out}$: Outflow rate constant

Inhibition

Disease Progression

Placebo Effect

Disease Status

Logistic Regression

PGA Score

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Latent Variable Indirect PK/PD Model

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

- Baseline probability: α_k

- Disease progression f_z(t) = βt

- 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)
(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)**
- \( h(t) = a\lambda t^{a-1} \exp(-\beta_0 Y_0) \)
- Depend on past observed data \( Y_0 \) 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
Initial Model Conditional VPC

90% P.I.  observed  median predicted

PGA <= 2  PGA <= 2  PGA <= 2  PGA <= 2
TRT 1  TRT 2  TRT 3  TRT 4

PGA <= 1  PGA <= 1  PGA <= 1  PGA <= 1
TRT 1  TRT 2  TRT 3  TRT 4

PGA = 0  PGA = 0  PGA = 0  PGA = 0
TRT 1  TRT 2  TRT 3  TRT 4

probability

time (weeks)

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Validation Using Phoenix 2 – Conditional VPC
Final Model with Combined Data

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Time (weeks):

- 0
- 50
- 100
- 150

Probability:

- 0.0
- 0.2
- 0.4
- 0.6
- 0.8

90% P.I.

- Observed
- Median predicted

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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