Pharmaceutical Statistics Journal Club
15th October 2015

Missing data sensitivity analysis for recurrent event data using controlled imputation

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Pharmaceutical Statistics, 13 (4):258-264

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Acknowledgements

– James Roger, LSHTM

– Mike Kenward, LSHTM

– Ben Hartley, Veramed
Outline

- DREAM trial: mepolizumab for severe uncontrolled eosinophilic asthma
- Analysis of recurrent event data
- De Jure and de Facto estimands
- Application of pattern mixture models to recurrent event data
- Options for modelling post-withdrawal period for discontinuations
- Results for DREAM trial
DREAM study design

Double Blind Treatment 52 Weeks

Total N=616

- Mepolizumab 75mg IV N=153
- Mepolizumab 250mg IV N=152
- Mepolizumab 750mg IV N=156
- Placebo IV N=155

Subjects discontinuing randomised treatment not followed up off treatment
Withdrawals over time
## Withdrawals

<table>
<thead>
<tr>
<th>Reason for withdrawal</th>
<th>Placebo N=155</th>
<th>75mg N=153</th>
<th>250mg N=152</th>
<th>750mg N=156</th>
</tr>
</thead>
<tbody>
<tr>
<td>Withdrawn</td>
<td>28 (18%)</td>
<td>24 (16%)</td>
<td>21 (14%)</td>
<td>23 (15%)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>11 (7%)</td>
<td>8 (5%)</td>
<td>2 (1%)</td>
<td>7 (4%)</td>
</tr>
<tr>
<td>Adverse event</td>
<td>6 (4%)</td>
<td>5 (3%)</td>
<td>8 (5%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>8 (5%)</td>
<td>6 (4%)</td>
<td>4 (3%)</td>
<td>4 (3%)</td>
</tr>
<tr>
<td>Investigator discretion</td>
<td>1 (&lt;1%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>4 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
DREAM trial: model for primary analysis

- Primary endpoint: frequency of clinically significant asthma exacerbations
- Primary analysis: negative binomial model
- Each person has own Poisson rate of events
  - As a set follow a gamma distribution across patients
- Variation among patients explicitly captured as part of the model
  - No “correction” needed
- Model allow for different lengths of follow-up for each patients
- Generalised linear model, can incorporate baseline covariates
Estimands: De Jure and De Facto

- De jure (efficacy) estimand: expected treatment effect if treatments were taken as specified in the protocol

- De facto (effectiveness) estimand: difference in outcome improvement for all randomized patients, assesses benefit of a treatment strategy relative to a control
DREAM trial

- Primary analysis: negative binomial model
  - Missing at random (MAR) assumption
    - conditional on the data observed (including covariates and data prior to withdrawal) unavailable data are randomly missing.
    - Implies future statistical behaviour of outcomes is the same for those who remain in the trial and those who withdraw conditional on their history
    - Addresses a De Jure estimand

- Need for alternative De Facto estimand
Pattern mixture models

- General framework described in earlier talk by Bohdana Ratitch et al
- Control-based imputation for longitudinal continuous data described by James Carpenter/James Roger/Mike Kenward in 2013 paper
  - Model post-withdrawal outcome for active (test) to reflect the behaviour of later outcomes on placebo (reference)
- Can this be applied to recurrent event data (exacerbations)?
Recurrent event trials: early withdrawals

- If a patient has $y_1$ exacerbations during period 1 and then withdraws
- We want to estimate $y_2$, the number of unobserved exacerbations, given what we have actually seen
Multinomial models (Roger/Kenward)

- Negative binomial is special case of negative multinomial model
- Conditional distribution of the missing values for partially observed negative multinomial data is also negative multinomial
- Missing data can be imputed using the appropriate negative multinomial models
- Numbers of events before and after withdrawal are seen as two periods with a joint negative multinomial distribution, with $Y_1$ observed and $Y_2$ unobserved
Impute unobserved exacerbations

For a given patient, distribution $Y_2|Y_1$ is a function of:
- Observed $y_1$
- Estimated dispersion (assumed same in both periods)
- Estimated mean (model predicted) rate period 1
- Imputed mean rate period 2
  - Options for this described on next slide

Multiple imputation
- Take a random sample from $Y_2|Y_1$, add this to the $y_1$ we observed for the patient
- Analyse the data using PROC GENMOD as usual
- Repeat analysis multiple times
- Combine estimates using Rubin’s rules
Imputing patient’s expected rate during period 2

Placebo patients imputed under MAR

<table>
<thead>
<tr>
<th>Method for Active Treatment</th>
<th>Period 1</th>
<th>Period 2</th>
<th>Residual from period 1?</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAR</td>
<td>Active</td>
<td>Active</td>
<td>Yes</td>
</tr>
<tr>
<td>Copy Reference (CR)</td>
<td>Placebo</td>
<td>Placebo</td>
<td>Yes</td>
</tr>
<tr>
<td>Jump to Reference (J2R)</td>
<td>Active</td>
<td>Placebo</td>
<td>Yes</td>
</tr>
<tr>
<td>Unconditional Reference (UR)</td>
<td>Active</td>
<td>Placebo</td>
<td>No</td>
</tr>
<tr>
<td>Delta methods</td>
<td>Active</td>
<td>Active - Delta</td>
<td>Yes</td>
</tr>
<tr>
<td>Specific off treatment say κ</td>
<td>Active</td>
<td>Kappa</td>
<td>No</td>
</tr>
</tbody>
</table>

– Can make imputation method depend on reason for withdrawal
DREAM: de jure and de facto estimands

**75mg IV vs. Placebo**
- De Jure (MAR) 0.52 (0.39, 0.69)
- De Facto (J2R) 0.56 (0.42, 0.76)
- De Facto (UR) 0.55 (0.41, 0.74)

**250mg IV vs. Placebo**
- De Jure (MAR) 0.61 (0.46, 0.81)
- De Facto (J2R) 0.64 (0.48, 0.86)
- De Facto (UR) 0.63 (0.47, 0.84)

**750mg IV vs. Placebo**
- De Jure (MAR) 0.48 (0.36, 0.64)
- De Facto (J2R) 0.53 (0.39, 0.71)
- De Facto (UR) 0.53 (0.39, 0.71)

**Notes:**
- MAR = Missing at Random, J2R = Jump to Reference, UR = Unconditional Reference
Conclusions

– Likelihood analyses produce De Jure estimands under MAR assumption
  – What would happen if patient continued on treatment
– Need De Facto (ITT) estimands
  – Compare results of initial randomisation
  – Requested by regulatory authorities
– One possible approach is to use controlled imputation for recurrent event data
References


