Impact of covariate misclassification on the power and type I error in clinical trials using covariate-adaptive randomization

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Properties of covariate-adaptive randomization

- Well balance important prognostic covariate
- More generalizable and convincing result
- Increase power for subgroup analysis
- Require correct specification of analysis model for hypothesis testing

• Covariate adjustment during analysis
  - Type of analysis: model based
  - Type of outcome: Dichotomized
  - Covariate adjustment in logistic regression
    - Precision
    - Efficiency

• Motivation
  ○ Interventional Management of Stroke III (IMS III)
    ▪ Stratified biased-coin randomization: Stroke severity
    ▪ Misclassification Rate: 2%, non-differential
    ▪ Primary analysis: True severity VS. Randomized severity
  ○ High-Dose Deferoxamine in Intracerebral Hemorrhage (Hi-DEF)
    ▪ Stratified biased-coin randomization: time from symptom onset to treatment
    ▪ Misclassification Rate: 27.3% and 6.3%, differential
    ▪ Primary analysis: Anticipated time window VS. Actual time window
• Impact of adjusting with misclassified covariates under covariate adaptive randomization.

## IMS III

<table>
<thead>
<tr>
<th>NIHSS STRATUM (RANDOMIZED)</th>
<th>NIHSS STRATUM (ACTUAL)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NIHSS 19 OR LOWER</td>
<td>NIHSS 20 OR HIGHER</td>
</tr>
<tr>
<td>N</td>
<td>% Randomized</td>
<td>% Randomized</td>
</tr>
<tr>
<td>448</td>
<td>98.03%</td>
<td>9</td>
</tr>
<tr>
<td>4</td>
<td>2.01%</td>
<td>195</td>
</tr>
<tr>
<td></td>
<td>1.97%</td>
<td>97.99%</td>
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</tbody>
</table>

## Hi-DEF

<table>
<thead>
<tr>
<th>TIME WINDOW (RANDOMIZED)</th>
<th>TIME WINDOW (ACTUAL)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual &lt;= 12 hours</td>
<td>Actual &gt; 12 hours</td>
</tr>
<tr>
<td>N</td>
<td>% Anticipated</td>
<td>% Anticipated</td>
</tr>
<tr>
<td>Anticipated &lt;= 12 hour</td>
<td>8</td>
<td>72.7%</td>
</tr>
<tr>
<td>Anticipated &gt; 12 hours</td>
<td>15</td>
<td>93.8%</td>
</tr>
<tr>
<td></td>
<td>6.3%</td>
<td>27.3%</td>
</tr>
</tbody>
</table>
Method

- **Simulation**
  - Regression based analysis: Logistic regression
    - 1 prognostic covariate: subject to misclassification
    - 1 perfect measured variable: treatment assignment
    - No interaction
    - Dichotomized outcome
  - Randomization schemes
    - Simple randomization
    - Covariate adaptive randomization:
      - Stratified Block Randomization
      - Stratified Biased-coin Randomization
Method

- Simulation
  - Scenarios
    - Fixed control group rate (40%) and treatment group rate (50%)
    - Varied covariate effect: -3 to +3 (OR: 0.064-23.2)
    - Varied misclassification rate: 0% to 40%
    - Type of misclassification: non-differential
Method

- Simulation
  - Models compared
    - Unadjusted model
    - Model adjusted with misclassified covariate
    - Model adjusted with corrected covariate
  - Operating characteristics evaluated
    - Bias
    - Power
    - Type I error rate
Result-Bias

Simple Randomization

Covariate adaptive Randomization

L. Fan, SD. Yeatts, W. Zhao; MUSC

Society for Clinical Trials, May 2014
Simple Randomization

Covariate adaptive Randomization

Result-Power

L. Fan, SD. Yeatts, W. Zhao; MUSC
Result-Type I error Rate

Simple Randomization

Covariate adaptive Randomization

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L. Fan, SD. Yeatts, W. Zhao; MUSC
Conclusion

- Impact on the estimate of treatment effect
  - Direction: Bias towards Null
    - Same direction of “bias” caused by unadjusting covariate
    - Adjusted estimate VS. unadjusted estimate
  - Magnitude
    - Misclassification rate: about 30% misclassification is almost the same as not adjusting the covariate.
    - The covariate effect on the outcome given the treatment effect

Conclusion

- Impact on power for detecting treatment effect
  - Randomization schemes do not have effect on power
  - Adjusting with corrected covariate minimize the power loss due to study design
  - The amount of power loss
    - Misclassification rate
    - Covariate effect on the outcome given the treatment
Conclusion

- **Impact on type I error rate**
  - Simple randomization: maintained
  - Covariate-adaptive randomization
    - Adjusting with corrected covariate: maintained
    - Adjusting with misclassified covariate: maintained
    - Without adjusting covariate: conservative
Discussion

- Under covariate adaptive randomization, adjusting randomized covariate is always recommended for final analysis
- Randomization scheme does not have an “add-on” effect on bias and power loss caused by covariate misclassification
- Attention should be drawn to correct the bias in estimating the effect of treatment and sample size reassessment with the presence of covariate misclassification
Questions?