(Re)Randomizing using baseline covariates in animal studies

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Motivation

- Randomization is a Pillar of Good Experimental Design

- Mice are not Men
  - Clinical Studies
    - Protocols, Regulators, Software, Literature, Design Aspects (e.g., multi-center, recruitment, sequential, disease stage), etc.
  - Animal experiments
    - Less Rigor, Scientist-led, Data (e.g., bodyweight), Speed, Spreadsheets, (Lack of) Blinding, Small Sample Sizes, ‘Nicer’ Endpoints
    - Some Common Designs: Two-sample, 1-way ANOVA, Dose Response, ‘Small’ Full Factorial-plus
      - Pre and Post Treatment Endpoints
      - Repeated Measure and Cross-Over are Less Common
Rerandomization: an Approach

  - Rerandomize Subjects based on Mahalanobis Distance
    - Resample Candidate Designs and Evaluate Balance Criteria
      - Identify Suitable Randomizations Based on Resampling Distribution
      - Analyze with a Randomization Test (not used)
  - Tiers for Covariates of Varying Importance
  - Extensions: Unequal Treatment Group Size, Rerandomized Block
    - ‘Block what you can, and rerandomize what you cannot.’
  - Theory & Pre/Post Test Application

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Early Clinical Development

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

Lock (2011)
Algorithm

• Core Idea

  - Distribution of F-test/MANOVA Test Statistics
  - User Selects Randomization Passing Pre-Set Threshold

• Covariate Tiers
  - 2 Levels: Regression Residuals

• Visual Diagnostics

Lock (2011)
Implementation

• Software: Shiny App
  – Data Calculations Outside of App
    • Average, Transform, Imputation, Covariate Interactions, etc.

• Exclusions
  – Repeated Measures, Sequential Designs, Interim Analyses
  – ‘Omics (n << p) or Ultra-small Group n

• Adaptations or Ad Hoc Adjustments
  – Unequal Sample Sizes, e.g., View 3 Groups in 2:2:1 Ratio as 5 Groups
  – Genotype, Yes/No Tumor Model
  – Cage Weight
  – Non-floating Point Numbers
Case Study: Bodyweight and Food Intake

Randomizing to Balance In Vivo Baseline Measurements

Data Upload

Upload your data here. Data must be in a comma-separated value format, i.e., as a .csv file. The first column must be a subject identifier (ID). The first row must contain label names for the ID and baseline measurements. After upload, a data preview panel will appear below.

Only numerical baseline measurements are supported in this app. We recommend capping the number of baseline covariates at five. Missing data are not allowed.

An introductory guide can be found here. Contact Don Bennett or Phillip Yates for additional information regarding the application or its interface. Questions regarding the website should be directed to Woody Burchett.

Note: Not for use in regulated or clinical studies.
Case Study: Bodyweight and Food Intake (cont.)

Randomize Treatments

Randomly allocate treatments while balancing for various baseline measurements using this tab. The user defines the number of treatment groups, sample size per group, and the baseline variables to include. The minimum group size is three subjects. An additional option is to define two tiers where the first tier contains the more important baseline covariate(s). After specifying the input parameters press "Generate Design" to perform the randomization. Once a randomization candidate has been identified summary plots, statistical comparison results, and the grouped data can be viewed using the "Select Summary" pull-down. Repeated clicks of the design button will generate new randomizations. The grouped data can be downloaded as a CSV file.

Contact Don Bennett or Phillip Yates for additional information regarding the application or its interface. Questions regarding the website should be directed to Woody Burchett.
Case Study: Bodyweight and Food Intake (cont.)

Select Summary
- Boxplots

Generate Design

Download Grouped Data

Early Clinical Development
Case Study: Bodyweight and Food Intake (cont.)

<table>
<thead>
<tr>
<th>Response</th>
<th>F Value</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bodyweight</td>
<td>0.0308</td>
<td>0.97</td>
</tr>
<tr>
<td>FoodIntake</td>
<td>0.0737</td>
<td>0.929</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal</th>
<th>Bodyweight</th>
<th>FoodIntake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Cage_01</td>
<td>189.12</td>
<td>1.88</td>
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<tr>
<td>Group 3</td>
<td>Cage_02</td>
<td>195.79</td>
<td>0.44</td>
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<tr>
<td>Group 3</td>
<td>Cage_03</td>
<td>189.49</td>
<td>2.68</td>
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<td>204.79</td>
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<tr>
<td>Group 1</td>
<td>Cage_06</td>
<td>213.83</td>
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</tbody>
</table>
Lessons

• Welcomed by Scientists and Lab Heads

• Introduce, Streamline, or Improve Randomization Process

• Training Needs are Minimal

• Unintended Consequences
  – Help Identify and Eliminate Extreme Observations
  – Brute Force Resampling and not a ‘Smart’ Artificial Intelligence App
  – Encourages (doesn’t Enforce) Balance Across Groups
  – Tiers are not needed
Alternatives

• Could Extend to also Balance Variability, e.g., Range

• Stratified Block Randomization, Minimization, Multivariate Matching, Optimal Block Designs, etc.
  – Large Literature for Clinical Trials

• Open Source or Commercial Software
  – R Libraries?
    • Optimal Design, Clinic, etc., Packages
  – JMP: Covariate Factor Option in Custom DOE Platform
Alternatives (cont.)

- Covariate Designs
  Cages 5 Row/6 Col plus Bodyweight and Food Intake

- Two Treatment Pair-Matched for 2 Correlated Covariates: Clustering (vs. D-Optimal)
Acknowledgments and References

• Acknowledgments

Shiny App: Woody Burchett
In Vivo Test Subject: Don Bennett

• References

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S. Hore, A. Dewanji, A. Chatterjee (2014), Design issues related to allocation of experimental units with known covariates into two treatment groups, JSPI
Thank You.

Questions?