(Re)Randomizing using baseline covariates in animal studies

Phillip Yates

May 15, 2018

Early Clinical Development

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT

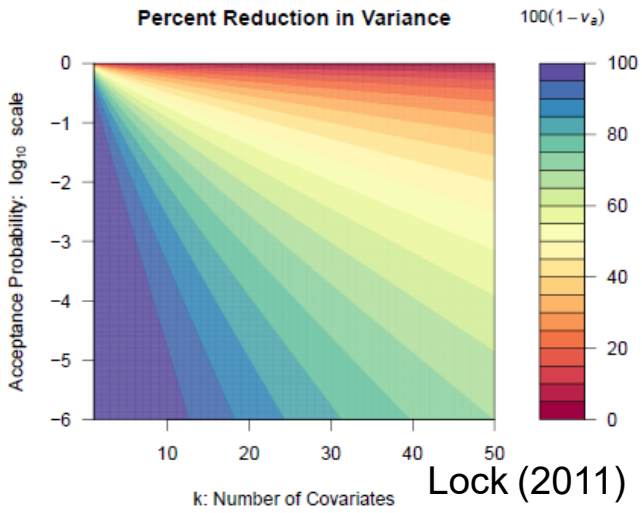
Motivation

- 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

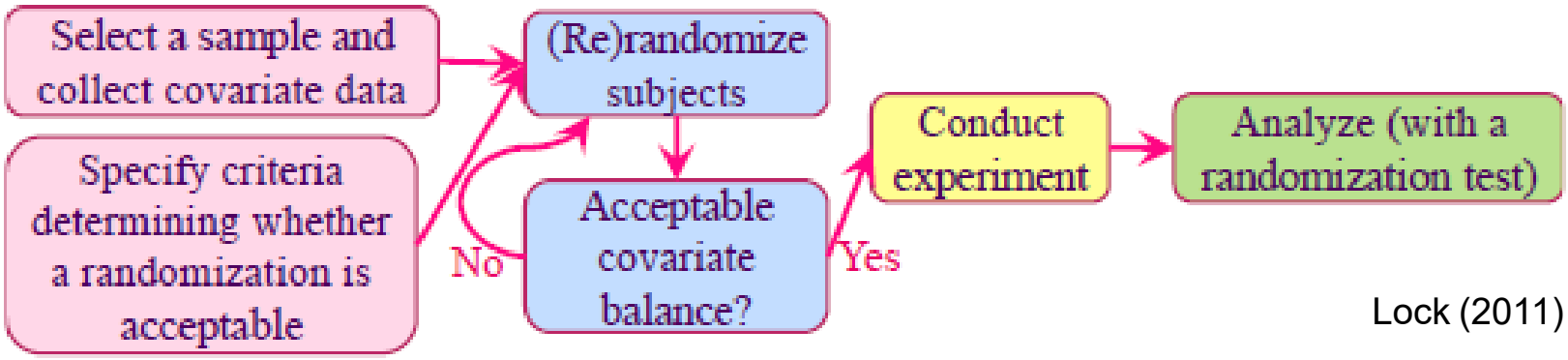
- Balance Covariates – K. Lock's PhD Thesis
  - Rerandomize Subjects based on Mahalanobis Distance
    - Resample Candidate Designs and Evaluate Balance Criteria
      - Identify Suitable Randomizations Based on Resampling Distribution
      - Analyze with a Randomization Test (not used)
    - Tiers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



Lock (2011)

Algorithm

- Core Idea



Lock (2011)

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

- Covariate Tiers
  - 2 Levels: Regression Residuals

- Visual Diagnostics

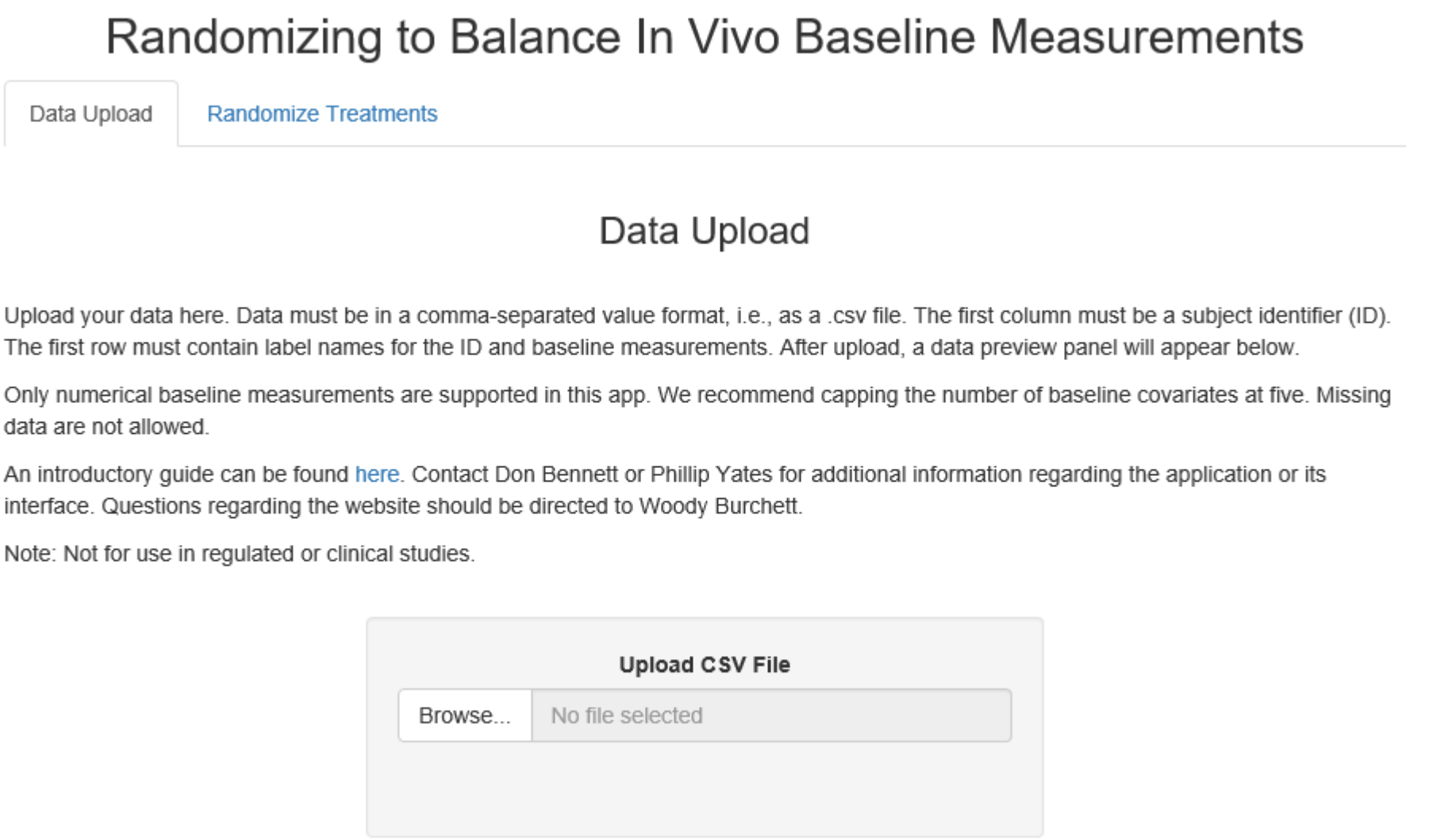
Implementation

- 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

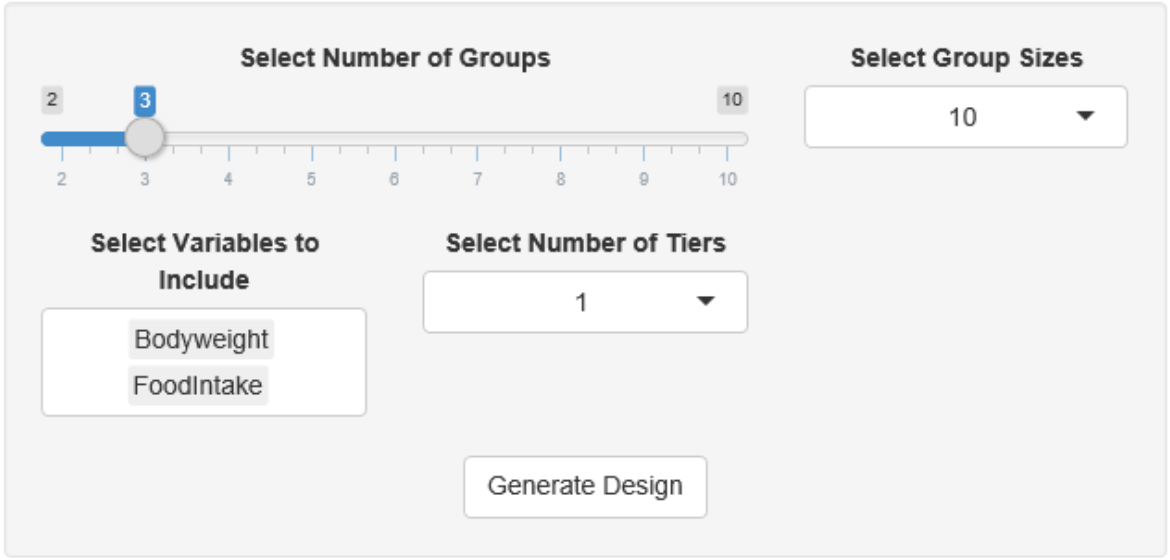


Case Study: Bodyweight and Food Intake (cont.)

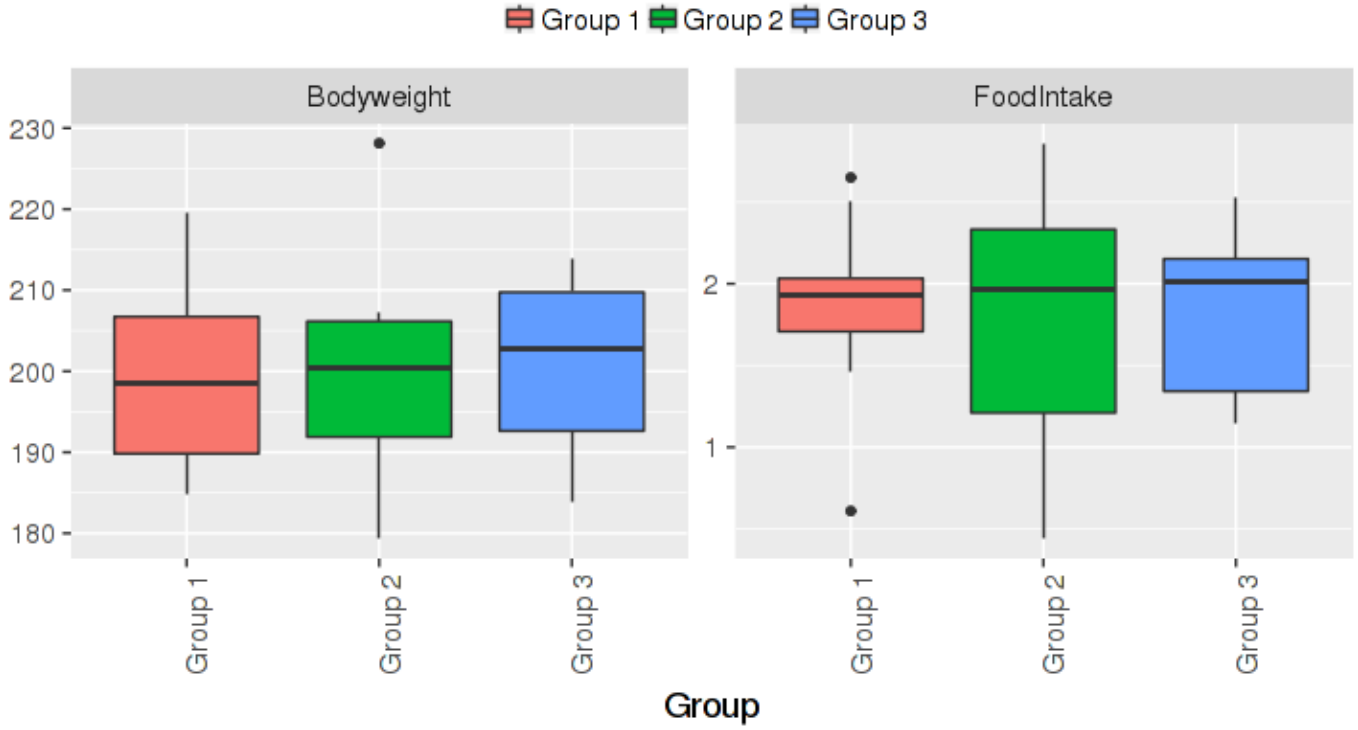
Randomize Treatments

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.

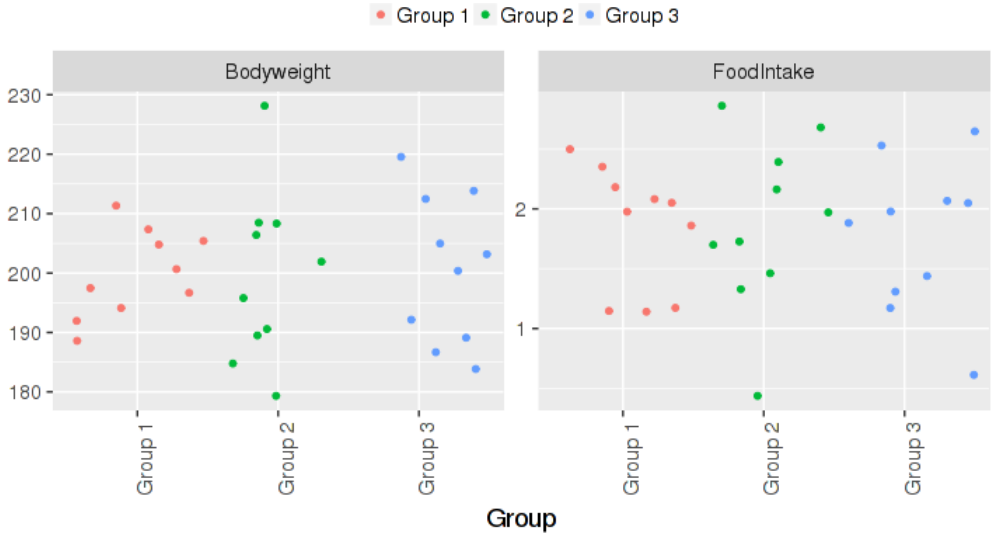
Contact Don Bennett or Phillip Yates for additional information regarding the application or its interface. Questions regarding the website should be directed to Woody Burchett.



Case Study: Bodyweight and Food Intake (cont.)



Case Study: Bodyweight and Food Intake (cont.)



Response	F Value	p-value
Bodyweight	0.0308	0.97
FoodIntake	0.0737	0.929

Group	Animal	Bodyweight	FoodIntake
Group 1	Cage_01	189.12	1.88
Group 3	Cage_02	195.79	0.44
Group 3	Cage_03	189.49	2.68
Group 2	Cage_04	206.4	2.39
Group 1	Cage_05	204.79	1.14
Group 1	Cage_06	213.83	2.53

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)

Custom Design

Responses

Factors

Add Factor | Remove | Add N Factors 1

Name	Role	Changes	Values					
Bodyweight	Covariate	Easy	185.81				222	
FoodIntake	Covariate	Easy	1.05				2.59	
Cage Column	Categorical	Easy	L1	L2	L3	L4	L5	L6
Cage Row	Categorical	Easy	L1	L2	L3	L4	L5	
Treatment	Categorical	Easy	Compound				No Compound	

Define Factor Constraints

Model

Main Effects | Interactions | RSM | Cross | Powers | Remove Term

Name	Estimability
Intercept	Necessary
Bodyweight	Necessary
FoodIntake	Necessary
Cage Column	Necessary
Cage Row	Necessary
Treatment	Necessary

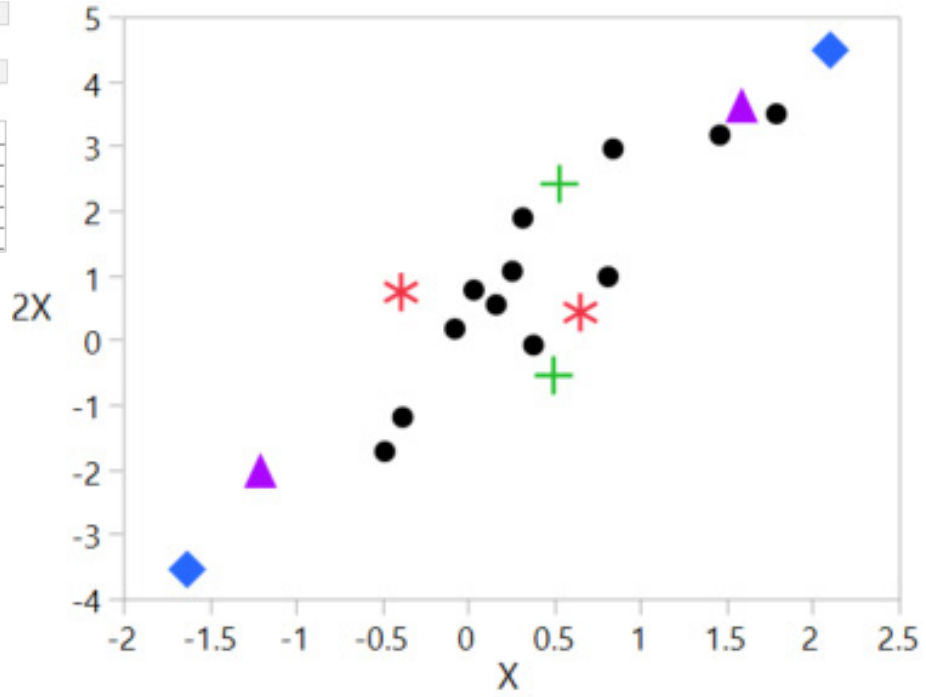
Alias Terms

Design Generation

☐ Enforce use of selected covariate rows

Number of Runs: 30

Make Design



Acknowledgments and References

- Acknowledgments

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

- References

K. Lock (2011), Rerandomization to improve covariate balance in randomized experiments, PhD Thesis, Harvard U.
K. Morgan & D. Rubin (2015), Rerandomization to balance tiers of covariates, JASA
K. Morgan & D. Rubin (2012), Rerandomization to improve covariate balance in experiments, AOS
Y. Lin, M. Zhu & Z. Su (2015), The pursuit of balance: an overview of covariate-adaptive randomization techniques in clinical trials, Contemporary Clinical Trials
N. Kallus (2017), Optimal *a priori* balance in the design of controlled experiments, JRSS-B
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?

Early Clinical Development

Pfizer WORLDWIDE RESEARCH & DEVELOPMENT

SCIENCE FOR LIFE-CHANGING IMPACT