Rerandomization in Clinical Trials

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Covariate Balance - Sex

- Suppose you get a “bad” randomization
- What would you do???
- Can you rerandomize???

5 Females, 15 Males

15 Females, 5 Males
Rubin: What if, in a randomized experiment, the chosen randomized allocation exhibited substantial imbalance on a prognostically important baseline covariate?

Cochran: Why didn't you block on that variable?

Rubin: Well, there were many baseline covariates, and the correct blocking wasn't obvious; and I was lazy at that time.

Cochran: This is a question that I once asked Fisher, and his reply was unequivocal:

Fisher (recreated via Cochran): Of course, if the experiment had not been started, I would rerandomize.
The Gold Standard

Randomized experiments are the “gold standard” for estimating causal effects, because they balance covariates between groups on average

BUT for any particular experiment, covariate imbalance is possible (and not unlikely!)

With just 10 independent covariates, the probability of a significant difference ($\alpha = .05$) for at least one covariate is $1 - (1-.05)^{10} = 40\%$!
Randomize subjects to treated and control.

Specify criteria determining when a randomization is unacceptable; based on covariate balance.

(Re)randomize subjects to treated and control.

Collect covariate data.

Check covariate balance.

RERANDOMIZATION

Conduct experiment.

Analyze results with a randomization test.

1) Collect covariate data
2) Specify criteria determining when a randomization is unacceptable; based on covariate balance
3) (Re)randomize subjects to treated and control
4) Check covariate balance
   - unacceptable
   - acceptable

3) Conduct experiment
4) Analyze results with a randomization test
Criteria for Acceptable Balance

We recommend using *Mahalanobis Distance*, $M$, to represent multivariate distance between group means:

$$M = (\bar{X}_T - \bar{X}_C)'[\text{cov}(X)]^{-1}(\bar{X}_T - \bar{X}_C)$$

Choose a threshold, $a$, and rerandomize when $M > a$
Distribution of $M$

$p_a = \text{Probability of accepting a randomization}$

Acceptable Randomizations

RERANDOMIZE
Covariates After Rerandomization

**Theorem:** If $n_T = n_C$, the $k$ covariate means are normally distributed, and rerandomization occurs when $M > a$, then

$$E\left( \overline{X}_T - \overline{X}_C \mid M \leq a \right) = 0$$

and

$$\text{cov}\left( \overline{X}_T - \overline{X}_C \mid M \leq a \right) = v_a \text{cov}\left( \overline{X}_T - \overline{X}_C \right).$$

$$v_a \equiv \frac{2}{k} \times \frac{\gamma\left( \frac{k}{2} + 1, \frac{a}{2} \right)}{\gamma\left( \frac{k}{2}, \frac{a}{2} \right)},$$

where $\gamma$ is the incomplete gamma function:

$$\gamma(b, c) \equiv \int_0^c y^{b-1} e^{-y} dy$$
Percent Reduction in Variance (PRIV):

$$\frac{\text{var}(\overline{X}_{j,T} - \overline{X}_{j,C} \mid \text{rerandomization}) - \text{var}(\overline{X}_{j,T} - \overline{X}_{j,C})}{\text{var}(\overline{X}_{j,T} - \overline{X}_{j,C})} = 1 - \nu_a$$
Percent Reduction in Variance

Acceptance Probability: $\log_{10}$ scale

$k$: Number of Covariates
Multiple Sclerosis Example

• Data from a clinical trial conducted by Biogen for a treatment for Relapsing-Remitting Multiple Sclerosis

• Does the drug cause people to have fewer relapses?

• 6 Covariates:
  • Age
  • Sex
  • Number of relapses in previous year
  • Expanded Disability Status Scale (made binary)
  • Presence of Gadolinium (Gd) enhanced lesions?
  • Presence of T2 lesions

• How could rerandomization have helped the design?
Covariate Balance

1000 pure randomizations
1000 rerandomizations, M < a with p_a = 0.001

-4 -2 0 2 4

Standardized Difference in Means, Treatment - Control
Theorem: If \( n_T = n_C \), the covariate means are normally distributed, and rerandomization occurs when \( M > a \), then for an outcome, \( Y \),

\[
E\left( \bar{Y}_T - \bar{Y}_C \mid M \leq a \right) = 0
\]

and

\[
\text{var}\left( \bar{Y}_T - \bar{Y}_C \mid M \leq a \right) = \left[ 1 - (1 - \nu_a)R^2 \right] \text{var}\left( \bar{Y}_T - \bar{Y}_C \right)
\]

where \( R^2 \) is the squared multiple correlation between the outcome, \( Y \), and the covariates, \( X \)

**Can improve power equivalent to increasing the sample size by up to \( 1/(1 - R^2) \)**
Analysis

• Rerandomization can drastically improve power!

• BUT to take advantage of this improvement, methods of analysis have to take the rerandomization into account

• Typical standard distributional based methods (such as a t-test) will overestimate the standard error, and will be too conservative (p-values will be too insignificant)

• To get an accurate p-value and Type I error rate, use a randomization test, where each simulated randomization follows the same rerandomization procedure used in the actual experiment
Extensions

• Tiers of covariates’ importance
• Block experiments
• Multiple treatment groups
• Unequal treatment group sizes
• Sequential assignment
• Generate a fixed number of randomizations and choose the one with the best balance
Emotional Brain

• Rerandomization used in the design of a clinical trial proposed to the FDA for a drug to improve female sexual satisfaction

• Patients enroll sequentially: rerandomize in blocks of B women at a time (B = 6 for this example)
  1. Randomize the first B women to enroll
  2. Treat these women with placebo or active treatment
  3. Wait for B more women to enroll
  4. Use rerandomization for these next B women, measuring overall covariate balance for all 2B women enrolled
  5. Treat these new B women with placebo or active
  6. Wait for B more women to enroll...

• For each rerandomization, generate a fixed number of randomizations and choose the best
• Rerandomization improves covariate balance between the treatment groups, giving the researcher more faith that an observed effect is really due to the treatment

• If the covariates are correlated with the outcome, rerandomization also increases precision when estimating the treatment effect, giving the researcher more power to detect a result

• Rerandomization can be used in a wide variety of experimental situations, and we’re expanding!

Covariate Balance: Actual Experiment

- Age
- Sex
- PrevRelapses
- EDSS
- GdLesions
- T2Lesions

Std. Diff. in Covariate Means, Treatment - Control
Covariate Balance: Random

The graph shows the standard difference in covariate means between the treatment and control groups. The covariates include Age, Sex, PrevRelapses, EDSS, GdLesions, and T2Lesions. The x-axis represents the standard difference in covariate means, with values ranging from -3 to 3.