Practical Guidance for Optimally Stratified Randomization for Sequential Entry Randomized Controlled Trials

Robert Greevy, Cole Beck,
and Jonathan Chipman

DEPARTMENT OF BIOSTATISTICS
VANDERBILT UNIVERSITY

Coauthors, Funding, No COI

Joint work with
Cole Beck and Jonathan Chipman
Department of Biostatistics, Vanderbilt

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Outline

Background and Motivation
The AAA Study
Matched Randomization
  for non-sequential or large batch entry
Matched Randomization
  for sequential entry studies - Jonathan

Why Randomize

Balance Covariates

Convince readers we didn't cherrypick our subjects

Justify our p-values

Justify our models

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Stratified Randomization

Toss a coin?
No.

Draw names from a hat?

AAA Study

Silber et al, 2004 (J. Clinical Oncology)

"The study was stratified on three variables: age at treatment (≤3 v >3 years at diagnosis of cancer), total cumulative anthracycline dosage (<300 v ≥300 mg/m2), and time from diagnosis (<10 v ≥10 years)."

AAA Study

	Enalapril (N = 69)	Placebo (N = 66)	P-value
Age at Dx	7.2	8.2	0.58
Years off Tx	7.2	7.7	0.67
Anthra' Dose	305	300	0.29
White (N)	63	51	0.024
Black	1	9	
Hispanic	4	3	
Other	1	3	

The solution – more hats

Stratified (block) randomization severely limits the number of covariates it can balance and forces categorization of continuous covariates.

But matching prior to randomization allows selecting the optimal set of strata.

Matched Randomization

- Match prior to randomization using a multivariate distance measure.

- Then assign one member of each pair to treatment with probability ½.

- Coin toss works when it is
- tossed once for each pair.

Matched Randomization

Benefits include[1,2,3]:

- Allows using all important covariates.
- Doesn't require forming exact matches (minimizing the ave dist between pairs).
- Can eliminate extreme imbalances.
- On average, better covariate balance (better Table 1's) & **Greater Power**.
- Easily used design based estimators.
- The usual estimators also work better.

1. Robert Greevy, Bo Lu, Jeff Silber, Paul Rosenbaum. Biostatistics. 2004.
2. Kosuke Imai, Gary King, and Clayton Nall. Statistical Science. 2009.
3. Kai Zhang and Dylan Small. Statistical Science. 2009.

Matched Randomization

- Can be used in cluster randomized trials[2,4]
- Can be used in k-arm trials
  (e.g. REACH Mayberry, et al.)
- Can incorporate the relative clinical[4] important of the covariates into the matching
- Can allow for missing data and control non-informative missingness[4]
- Can be used in sequential entry trials, but this is in need of further development

2. Kosuke Imai, Gary King, and Clayton Nall. Statistical Science. 2009.
4. Greevy, et al. Biostatistics. Pharmacoepidemiol Drug Safety. 2012.