# Randomization in Randomized Trials: More Than Just Random Numbers

Naihua Duan, Ph.D.
UCLA
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# Overview

- RCT has been the gold standard for the evaluation of health care procedures
- Randomized assignment is *expected* to balance prognostic factors across treatment arms
  - *Actual* balance fluctuates randomly
  - Stratification and blocking might help enhance actual balance
- Concealment of assignment prior to enrollment, to avoid protocol subversion and selection bias

# Set Up

- Real time enrollment of participants, randomize each participant after enrollment
- Two treatment arms (experimental treatment vs. control)
- Equal target sample size across arms

# Why Balance?

| Tx Arm | Gen-der | Out-come | n1 | Arm Out-come | n2 | Arm Out-come |
|---|---|---|---|---|---|---|
| Exp | F | 100 | 25 | 70 | 25 | 67 |
| | M | 40 | 25 | | 30 | |
| Ctrl | F | 80 | 25 | 50 | 25 | 53 |
| | M | 20 | 25 | | 20 | |

True Treatment Effect = 20

With 20/30 imbalance in one gender, estimated treatment effect = 14, off by 6 (30%)

# 20/30 Is Plausible

- 50 females, 50 males
- Randomize each individual 50/50
- Expect 25 females, 25 males in each arm
- One in five chance to be lopsided 20/30 or 30/20 or worse, among males
  - $N \sim \text{bin}(50, 0.5)$
  - $P(N \leq 20 \text{ or } N \geq 30) = 20.26\%$
  - $E(N) = 25$, $SD(N) = 3.54$;
  - $N = 20$ (30) is 1.41 SD away from the mean

# Need to Enhance Balance?

- Imbalance is more problematic with small sample sizes within stratum
- Imbalance is often a concern for moderate or small studies (n < 200 overall)
- For large studies, balance is usually fine with n ≥ 100 per stratum
  - Watch out for small, idiosyncratic subgroups

# Stratify By Gender?

- With simple randomization, stratification does not enhance balance of covariates
- In order to enhance balance beyond natural random fluctuation, some form of constraint needs to be imposed on the randomization procedure. The most common procedure is the randomized block design.

# Randomized Block Design (I)

- Block size 2:
  - Randomize first participant in each block, assign next participant to the other arm
  - Next participant starts a new block
  - Perfect balance up to ±1 (if there is an incomplete block)
  - 50 females, 25 blocks, guaranteed 25/25 balance

# Randomized Block Design (II)

- Block size 2k (k slots for each arm):
  - Randomize first participant in each block with equal probability to each arm
  - Randomize next participant according to remaining slots, say, with probability (k-1)/(2k-1) to experimental arm if the first participant was assigned to experimental arm
  - Continue until all k slots for one arm is filled; assign all remaining participants in the block to the other arm.
  - Start new block after randomizing 2k participants
- Balance guaranteed for full blocks, some imbalance might remain for incomplete blocks

# Randomized Block Design (III)

- Randomized block design might be vulnerable to protocol subversion and selection bias
- Smaller block sizes especially vulnerable
- With block size 2, the assignment for the second participant in the block can be predicted perfectly. This knowledge might lead to selective enrollment.

# Protocol Subversion

- Knowledge of assignment can affect enrollment, and might result in selection bias
  - Patient might choose not to enroll if she does not like the assignment
  - Recruiter might choose not to enroll a patient if she believes the assignment is not suitable for this patient
  - Data manager might choose not to enter an assignment into the database if…
- Motivation for subversion: self-interest, altruism…?
- Challenge for the principle of equipose

# Canadian National Breast Screening Study

- Unconcealed "allocation book" accessed by nurse or study coordinator to write in name of patient in the next available line associated with a treatment
- Randomization occurred after physical exam at 12 of 13 sites
- With the next assignment and patient condition apparent, subversion of randomization is possible
- Significant baseline imbalance was found across arms
- Bailar & MacMahon (1997), Boyd (1997)

# Concealment of Randomized Assignment

- Withhold knowledge of assignment until after enrollment (or beyond enrollment, if trial is blinded)
  - Use of sealed envelope to be opened after enrollment
  - Call-in to data coordinating center to obtain assignment
  - Log in to data coordinating center website to obtain assignment

# Subverting the Concealment

- Recruiters' attempts: "Accounts of deciphering included gaining information from pre-enrolment checks on bulletin boards, opening unsealed assignment envelopes, holding translucent envelopes up to the light, opening many envelopes that were not sequentially numbered until the desired treatment was found, holding opaque sealed envelopes to the 'hot light' (intense incandescent bulb) in the radiology department, using the appearance of tablets or labels on sequentially numbered drug containers, and obtaining the next few allocations at once." (Marcus 2001)
- Prediction of assignment from pattern of previous assignments
  - Blocked randomization with small block size is especially vulnerable
- Data managers' privileged access to assignment database?


Deciphering the allocation concealment scheme

In: Schulz KF, Grimes DA. Allocation concealment in randomised trials: defending against deciphering. Lancet. 2002 Feb 6;359(9306):614-8.

# Defending the Concealment

sequentially numbered, opaque sealed envelopes; pharmacy controlled[,] numbered or coded containers; central randomization – e.g. by telephone to a trial office – or other method whose description contained elements convincing of concealment – e.g. a secure computer-assisted method…
central randomization continues to be an excellent allocation concealment approach, effective trial procedures need to be established and followed. Researchers should at least specify the mechanism for contact – e.g., telephone, fax, or e-mail – the stringent procedures to ensure enrolment prior to randomization, and the thorough training of individuals at the central randomization office. All these details should be addressed when doing a trial and when writing a trial report."
(Schulz and Grimes 2002)

# Randomized Block Design (IV)

- Randomize block sizes to reduce the chance for the pattern to be predicted
- Might still allow partial predictability
- Hacker's prediction model does not have to be perfect in order to lead to selection bias
  - With any block size, adjacent assignments are always negatively correlated; just play the opposite will go a long way towards predicting the next assignment

# Detecting the Subversion

- Compare baseline characteristics across arms
- Berger-Exner test for selection bias in randomized block designs
  - Regress outcome on treatment group and P(E), the predicted probability for the assignment to the experimental arm, based on previous assignments
  - With block size 2, P(E)=0.5 for first participant in each block, P(E)=0 (1) for second participant if first participant is assigned to experimental (control) arm
  - Significant relationship between P(E) and the outcome is evidence for subversion and selection bias attributable to deciphering the randomized block design
  - Can also be used for prognostic factors?

# Recommendations (I)

- Blocked randomization should be considered, especially for small studies or small strata, if stratifying variables are believed to be highly predictive of outcome
- Centralized, web-based randomization is preferred to enveloped based or telephone based protocols
  - Extensive testing and record keep is necessary
- Thorough planning and monitoring of centralized protocol is essential to its success

# Recommendations (II)

- From the very beginning of a randomized trial, engage a senior biostatistics faculty with extensive experience in randomized trials to lead and guide the design and implementation of the randomization procedure
- Include the importance of randomization concealment in the training for field and data management staff

# Recommendations (III)

- Maintain consistent and regular documentation of randomization protocol and its implementation, such as records of all contacts with the centralized randomization website, to establish an audit trail that can be monitored to detect irregularities
- Establish individual login accounts with individual passwords for staff members responsible for accessing the randomization website to conduct randomization activities, to facilitate individual accountability

# Recommendations (IV)

- On a regular basis, conduct interim analyses of randomization records, such as comparison of baseline characteristics across arms, and Berger-Exner's test for prognostic factors (and outcomes if data are available), to detect potential problems

# References


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