INTRODUCTION TO THE PRINCIPLES AND PRACTICE OF CLINICAL RESEARCH

Issues in Randomization

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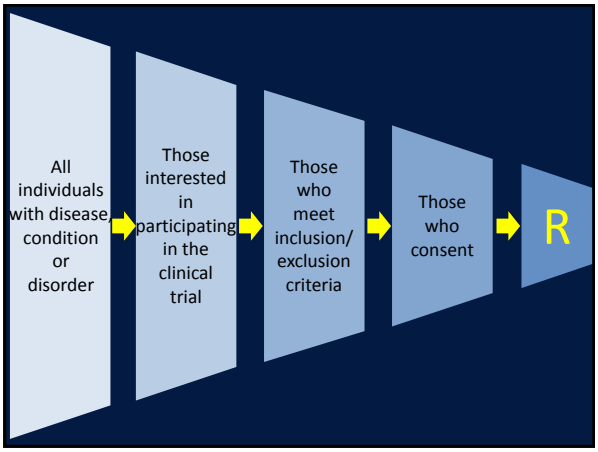

Outline

- What is "random"?
- What is randomization?
- Why randomize?
- Whom/what to randomize?
- How to randomize?
- Miscellaneous points
- Recommendations

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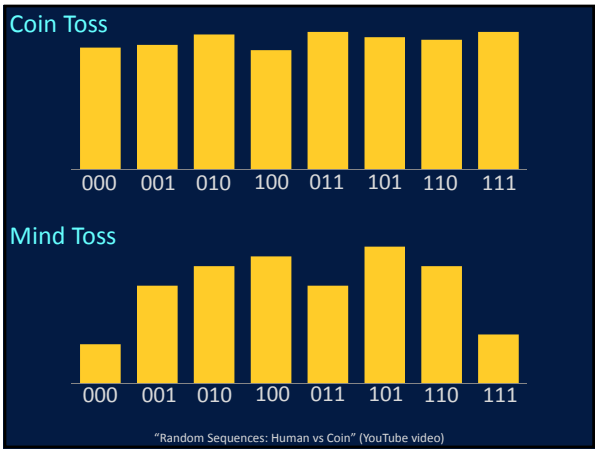
What is "random"?

Having no specific pattern

Unpredictable



"Random Sequences: Human vs Coin" (YouTube video)

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What is randomization?

In the clinical trial context, randomization is a method based on (known) chance alone, by which eligible and consented participants are assigned to one of the study interventions

The participant's time of randomization is key:

- Pre-randomization (baseline)
- Post-randomization

What is randomization?

- Which treatment condition is assigned is a result of chance
- Each possible assignment has a known chance of being selected
- Which treatment condition will be assigned is unpredictable

Randomization Ratio

1:1

1:1:1

1:2

1:1:2

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Why randomize?

- Keeps treatment allocation free from *selection bias*
- Balances intervention groups with respect to *known and unknown* baseline characteristics that may influence the outcome
- Most importantly, allows to attribute differences in outcomes to differences in efficacy of the treatments under study (causality)

Why randomize?

Randomized Controlled Trials (RCTs)
vs.
Observational studies

Confounding factors

Confounding Factors (or Effect)

Two-site clinical trial:

Site 1, in Los Angeles, California, happens to be only for men, gets assigned Treatment *A*

Site 2, in Boise, Idaho, happens to be only for women, gets assigned Treatment *B*

Result: Treatment *B* is better than Treatment *A*

Any factor confounded with treatment?

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Whom/what to randomize?

- Participant (most common)
- Provider (e.g. doctor, nursing station)
- Locality (e.g. hospital, school, community)

Johnson 2013

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How *not* to randomize?

- Birth date
- Last digit of the medical record number
- Odd/even hospital room number

Johnson 2013

How to randomize?

Randomization Methods

1) Simple randomization
2) Permuted-block randomization
3) Stratified randomization
4) Cluster randomization
5) Adaptive randomization

1) Simple Randomization

Each participant is randomly assigned to a treatment with a known probability, regardless of the treatment assignments of other participants

Example:

Toss a coin: H → new intervention
T → placebo control

How to implement simple randomization

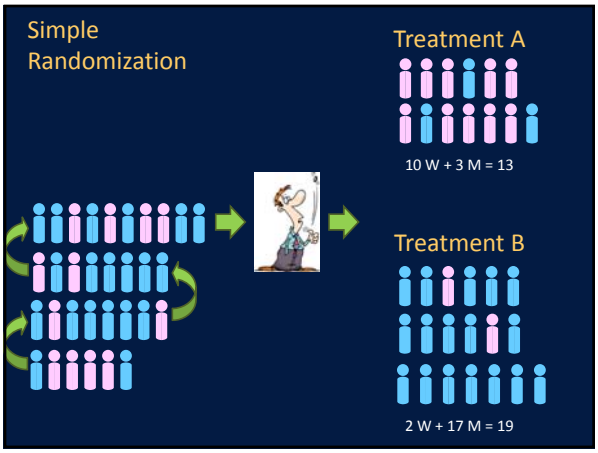
1) Low-tech: toss a coin (nobody does it this way)
2) Hi-tech: use computer programs (free or commercial)
   http://www.randomizer.org/form.htm (free)

Simple Randomization – Pros

- Easy to understand
- Simple to implement

Simple Randomization – Cons

- Significant deviations from equal assignments may happen by chance
- Significant imbalances in *important* baseline characteristics (e.g. gender) may happen by chance

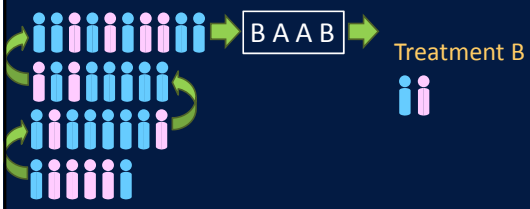


2) (Permuted) Block Randomization

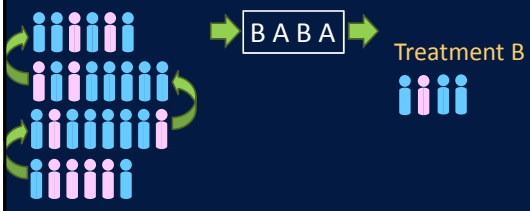
Every block of X new participants are randomly and equally assigned to treatments *A* and *B*
X = block size

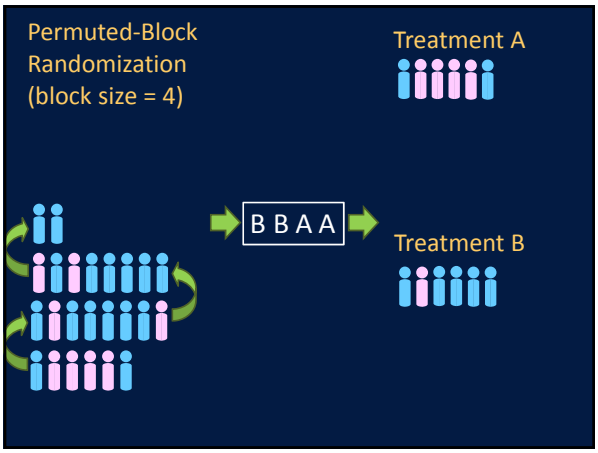
Example:
Block size of 4 → 6 possibilities:
AABB, *ABAB*, *BAAB*, *BABA*, *BBAA* and *ABBA*

Permuted-Block Randomization (block size = 4)



Permuted-Block Randomization (block size = 4)





How to implement block randomization

1:1
→ block size 4 (*AABB*), 6 (*AAABBB*), 8 (*AAAABBBB*) …

1:1:1
→ block size 6 (*AABBCC*), 9 (*AAABBBCCC*) …

1:2
→ block size 3 (*ABB*), 6 (*AABBBB*), 9 (*AAABBBBBB*) …

1:1:2
→ block size 4 (*ABCC*), 8 (*AABBCCCC*),
12 (*AAABBBCCCCCC*) …

(Permuted) Block Randomization

Block size > # of interventions

Known block size vs. masked (blinded) block size

Fixed block size vs. random block size

How to implement block randomization

Example:

Random block size of 4 or 6:

ABAB → BABBAA → BBAABA → BAAB → BABABA → AABB → ABAB → AABBAB → AABB → …

(Permuted) Block Randomization – Pros

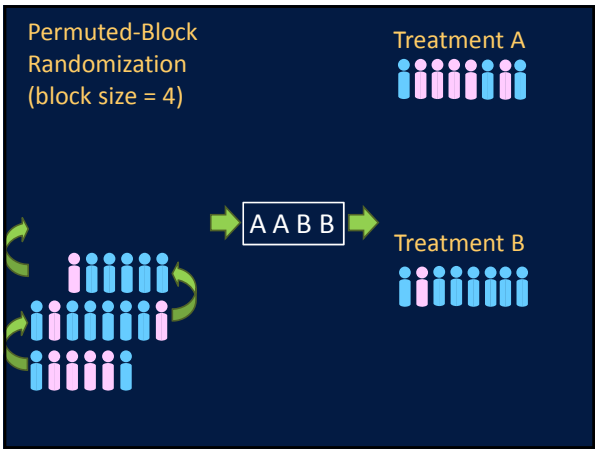
A perfect assignment balance will happen after X (block size) participants are randomized

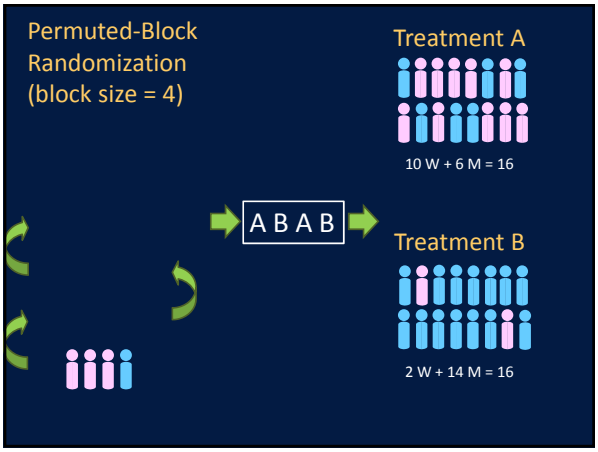
If time influences outcome (trends over time), a perfect assignment balance happens after short periods of time

(Permuted) Block Randomization – Cons

In *fixed* block size randomization, if block size is known, and intervention received is not masked, the assigned intervention can be predicted for the last person in the block

This is not the case in *random* block size randomization





(Permuted) Block Randomization – Cons

As with simple randomization, significant imbalances in important baseline characteristics (e.g. gender) may still happen by chance

3) Stratified Randomization

Stratification variable (or factor) = important *baseline* characteristic (e.g. gender) that *may* influence (predict) participant outcomes

Strata = different levels of the stratification variable, e.g. males and females (2 strata)

Examples of stratification variables: site, gender, age group, severity of disease

Randomization is performed separately within each stratum to achieve treatment assignment balance within each stratum

How to implement stratified randomization

Example:

Block randomization (block size=4) with stratification by site (clinical center)

Site 1: *AABB* → *ABAB* → *BAAB* → *BABA* → …

Site 2: *ABAB* → *BABA* → *ABBA* → *BAAB* → …

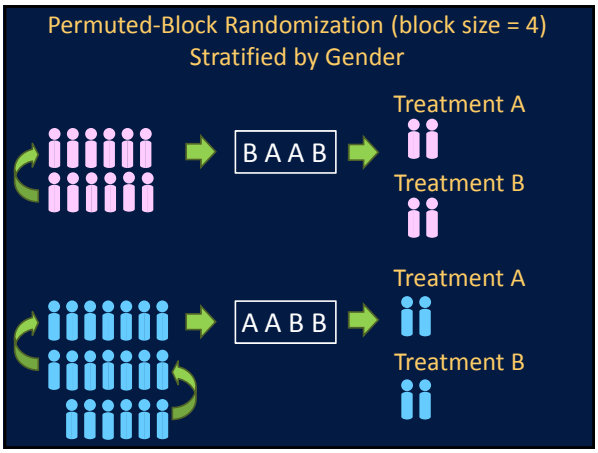
Site 3: *ABBA* → *BAAB* → *ABAB* → *BABA* → …

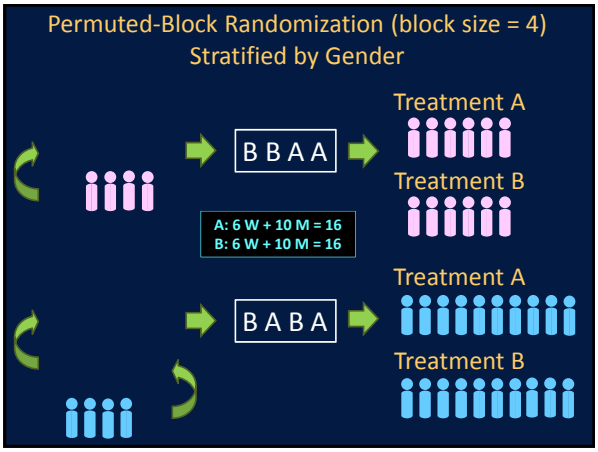
etc…

How to implement stratified randomization

Example:

Block randomization (block size=4) with stratification by gender





Stratified Randomization – Pros

Within each stratum (e.g. male/female), there is balance between the treatment groups, e.g. as many men in Treatment *A* as in Treatment *B*, and as many women in Treatment *A* as in Treatment *B*

Do not confuse with:

~~Within each treatment group, there is balance between strata, e.g. as many men as women in Treatment *A*, and as many men as women in Treatment *B*~~

Stratified Randomization – Cons

The number of cells can increase very rapidly with just a few stratification factors

Example:
4 stratification factors:
Site (3), gender (2), age (3), severity of disease (2)

Number of cells = 36 (3x2x3x2)

Randomization is conducted within each cell

4) Cluster Randomization

A cluster randomization trial is one in which intact social units, or clusters of individuals, rather than individuals themselves, are randomized to different intervention groups.

Donner & Klar 2000

Examples of clusters
Household, neighborhood, classroom, school, worksite, physician, clinic, hospital

Outcome measure is usually at the participant level

Why cluster randomization instead of regular individual randomization?

- Individual randomization may be impractical or impossible
- Cluster randomization prevents contamination
- Cluster randomization may be more convenient or economical

How to implement cluster randomization

Same as individual randomization, except that the unit of randomization is the cluster

Matching clusters before randomization

Cluster Randomization – Pros

- More feasible in some cases
- Minimizes contamination
- More convenient
- Cheaper

Cluster Randomization – Cons

- Unit of analysis (sample size)
- Number of participants in each cluster
- Intra-class (intra-cluster) correlation coefficient (ICC)

Fixed allocation algorithm

vs.

Adaptive methods or dynamic allocation

5) Adaptive Randomization

Minimization (covariate-adaptive allocation):
Changes the allocation probabilities to minimize any imbalances that have occurred by chance with respect to important baseline factors

Response-adaptive allocation:
Responses of participants enrolled to date change the allocation probability of the next assignment

How to implement adaptive randomization

Complex – need expertise and software

For minimization, *baseline characteristics* need to be quickly measured and entered into database

For response-adaptive, *assessments* need to be quickly measured and entered into database

Adaptive Randomization – Pros

Minimization:
May be more efficient than stratified randomization when sample size is small relative to the number of stratification factors (or cells)

Response-adaptive allocation:
Maximizes number of participants on the more promising treatment

Adaptive Randomization – Cons

Implementation and statistical analysis are more complex

International Conference on Harmonization (ICH) E9 Statistical Guidance document withheld judgment

European Medicines Agency's (EMA) Committee for Proprietary Medicinal Products (CPMP) 2003 document strongly discouraged its use

U.S. FDA provided guidance on its use

Shaw et al. 2012

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Threats to the Integrity of Randomization

- Exclusion of participants from final statistical analysis

Shaw et al. 2012

ITT vs. Per-Protocol Analysis

ITT
Intention-to-treat (or intent-to-treat)
= include in the analysis all participants who were randomized
= "once randomized, analyzed"

Per-protocol
Include in the analysis a select subgroup *as stated in the protocol*, e.g. those who took at least 80% of their medicine, or those who attended at least 75% of psychotherapy sessions

Threats to the Integrity of Randomization

- Exclusion of participants from final statistical analysis
- Large number of participants with missing primary outcome

Shaw et al. 2012

Is this a good randomization method?

Step 1: Create two groups of equal size

Step 2: Toss a coin to determine which group is assigned to which treatment

Is this a good randomization method?

Step 1: Toss a coin to determine the first treatment assignment

Step 2: After the first assignment, alternate between A and B

For example: ABABABABABABABABABABA…

Is this a good randomization method?

On Mondays, Wednesdays and Fridays, assign Treatment *A*

On Tuesdays, Thursdays and Saturdays, assign Treatment *B*

What is the connection between randomization and predictability?

One of the main goals of randomization is to prevent the ability to predict the next participant's treatment assignment

What is the connection between randomization and blinding?

Randomization protects from selection bias

Blinding (masking) protects from clinician assessment bias and participant response bias

What is the connection between randomization and intention-to-treat?

Without ITT analysis, the benefits of randomization are significantly weakened

What is the connection between randomization in a clinical trial and random sampling for a survey?

One main goal of randomization in a clinical trial is to balance known and unknown baseline characteristics

For surveys, the purpose of random sampling or random selection is to obtain a representative sample

What is the connection between randomization and equipoise?

Randomization is ethical as long as there is equipoise

What is the connection between randomization and statistical analysis?

The data analysis performed at the end of the study should reflect the randomization process actually performed.

Friedman et al. 2010

For example, stratification variables should be included in the statistical model

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Recommendations
(for common randomization methods)

- Use computer program or online tools
- Use permuted-block randomization with small random block size (<10)
- For multi-site clinical trials, use *site* as a stratification variable and in the statistical model
- Do not use too many stratification variables (≤4)
- Unless necessary, avoid adaptive randomization methods

Recommendations
(for complex randomization methods)

Consult with a biostatistician

Implementation Recommendations

1) Make it possible to reproduce the string of treatment assignments
2) Document randomization method used
3) Put in place features that prevent treatment assignment until conditions for entry into the trial are fully satisfied
4) Mask (blind) assignments to everyone concerned
5) Make it difficult (impossible) to predict future assignments from past assignments
6) Put in place procedures for monitoring departures from established protocols

Shaw et al. 2012

The End

Thank you for your attention
I hope this was worth your time

References (1 of 1)

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Questions / Comments