July 21 - 24, 2021 | Garki Hospital Abuja | Resource Person

Research Methodology Boot Camp

with Epi Info Training

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Target Audience Clinical Researchers, Post-Part 1 Residents, and Others

Important Information

- Limited slots are available on a first come, first served basis
- Laptop running Windows 10 required
- Organized as morning lecture sessions and afternoon hands on coaching sessions

Highlights

- Research Methodology
- Research Design
- Data Management
- Sample Size Calculations
- Test Statistics
- Interpretation of Results
- Report Writing
- Hands-on training sessions
- Statistical consulting sessions

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Randomization and Blinding

Introduction

- **Randomization** is a process by which each participant has the same chance of being assigned to either intervention or control.
    - The toss of a coin, in which heads indicates intervention group and tails indicates control group.
- Even in more complex randomization strategies, the element of chance underlies the allocation process.
- Neither trial participant nor investigator should know what the assignment will be before the participant's decision to enter the study.

Experimental bias

- Selection bias
  - The allocation process is predictable e.g. the decision to enter a participant into a trial may be influenced by the anticipated treatment assignment.
- Accidental bias
  - Allocation to treatment groups does not achieve balance on risk factors or prognostic covariates.

> Randomization tends to produce study groups comparable with respect to known as well as unknown risk factors, removes investigator bias in the allocation of participants, and guarantees that statistical tests will have valid false positive error rates.

Why randomize participants?

- **Eliminate selection bias**
  - Guarantee an unbiased treatment assignment (i.e., take the assignment decision out of the hands of the investigator), so that treatments are selected for participants independent of other prognostic factors, thus eliminating selection bias.

Why randomize participants?

- **Reduce accidental bias**
  - Help ensure balance of known and unknown risk factors or prognostic covariates between treatment groups so that on average no treatment has an unfair advantage.

Why randomize participants?

- **Help assure validity of statistical tests** that are used to compare treatments; e.g., need independence of measurement error and absence of confounders (i.e., things other than group membership that may cause observed differences).

How do we get random numbers?

- **Random number table** – a list of random digits consisting of a list of digits constructed by a process designed to satisfy the following 2 conditions:
    1. In any predetermined geographic position in the table any one of the 10 digits 0 through 9 has probability 1/10 of occurring (equal probability).
    2. The occurrence of any specific digit in any predetermined geographic position in the table is independent of the occurrence of specific digits in other positions in the table (independence).

How do we get random numbers?

- **Random number generator**
  - Many statistical packages, e.g., SAS, Stata, R, SPSS, Excel, etc. can be used to generate a large number of random numbers (based on uniform distribution).

General rules to follow

- Assignment is unknown to all persons until needed for treatment initiation
- Future assignments cannot be predicted
- Assignment probabilities are predetermined
- The allocation sequence is “reproducible”—thus, a departure from the assigned allocation sequence can be detected, e.g., when monitoring the RCT, in audits, etc.

Randomization methods

- Fixed allocation randomization
- Adaptive randomization

Fixed allocation randomization

- Fixed allocation procedures assign the interventions to participants with a prespecified probability, usually equal, and that allocation probability is not altered as the study progresses.
- Three types of fixed allocation randomization
  - Simple
  - Blocked
  - Stratified

Simple randomization

- Leave to chance the balancing of treatment A and treatment B (completely random)
- Method A: Use random number table.
- Method B: Use random number generator.

Simple randomization

Advantages

- Easy to implement
- Satisfies all criteria for randomization

Disadvantages

- At any point in the randomization, including the end, there could be a substantial imbalance

How often are large imbalances likely to occur?

- If 20 participants are randomized with equal probability to two treatment groups, the chance of a 12:8 split (i.e., 60% A, 40% B) or worse is approximately 50%.
- For 100 participants, the chance of the same ratio (60:40 split) or worse is only 5%.

Blocked randomization

- Subjects are divided into **blocks** according to the chronological time in which they enter the study and are randomly assigned to treatment A or treatment B such that there is balanced allocation between treatments within each block.
- Blocking is a restriction on the randomization over time.

Blocked randomization

Advantages

- Assures equal numbers of patients recruited to each treatment group throughout the recruitment period.
- Controls for chance imbalances between treatment groups on important patient characteristics which may change during the course of recruitment, especially for trials that have a long recruitment period. e.g., patients from different hospitals, different doctors treating

Blocked randomization

Disadvantages

- Prediction of future assignments.
  - (Never state the block size in the protocol.)
- It's more work to implement a block design, depending on how complicated the blocking becomes.

Blocked randomization

- Example: 20 subjects; 2 treatments A and B.
- First decision is “How big are the blocks?”
  - For example, blocks of size 4 (4 subjects per block)
  - Need 20 ÷ 4 = 5 blocks
  - Each block has 4 subjects, 2 assigned to A and 2 to B
  - After 4 subjects have been randomized, there will be 2 on A and 2 on B
- After each block, there will be equal numbers on A and B up to that point

Blocked randomization

- What are permuted blocks?
  1. Start with 2 As and 2 Bs
  2. How can these 4 people be ordered?

AABB	ABAB	ABBA
BBAA	BABA	BAAB

- These are the 6 permutations of 2 As and 2 Bs
- These are all the possible permuted blocks (of size 4)

Stratified randomization

- Separate randomization performed for separate strata that are defined using baseline characteristics.
- Ensures that the randomized groups are not imbalanced on the stratification variable.
    - Reduces or eliminates variation in the outcome measure due to the stratification variables
- Allows for the statistical analysis to account for variation in the outcome measures among strata.
    - Permits valid subgroup analyses

Stratified randomization

- For any single study, especially a small study, there is no guarantee that all baseline characteristics will be similar in the two groups.
- Stratified randomization requires that the prognostic factors be measured either before or at the time of randomization.
  - If a single factor is used, it is divided into two or more subgroups or strata.
  - If several factors are used, a stratum is formed by selecting one subgroup from each of them.
  - The total number of strata is the product of the number of subgroups in each factor.

Stratified randomization

- The stratified randomization process involves measuring the level of the selected factors for a participant, determining to which stratum she belongs and performing the randomization within that stratum.

Stratified randomization

What factors do you stratify on?

- Baseline factors strongly associated with the outcome.
- In a multicenter study, [almost] always stratify on ‘center’ (or ‘clinic’).
  - Subjects from different centers may have different baseline characteristics.
  - Standard of treatment may vary from center to center.
  - Each center represents a replicate of overall trial.
- Stratifying variables should be easily observed, measured prior to randomization, and relatively free of measurement error.

Stratified randomization

> Suppose an investigator wants to stratify on age, sex, and smoking history.

Age	Sex	Smoking history
1. 40-49	1. Male	1. Current smoker
2. 50-59	2. Female	2. Ex-smoker
3. 60-69		3. Never smoked

- Thus, the design has 3 × 2 × 3 = 18 strata

Stratified randomization

- Within each stratum, the randomization process itself could be simple randomization.
- In practice most clinical trials use some blocked randomization strategy.
    - Under a simple randomization process, imbalances in the number in each group within the stratum could easily happen and thus defeat the purpose of the stratification.

Stratified randomization

Strata	Age	Sex	Smoking	Group assignment
1	40-49	M	Current	*ABBA BABA* …
2	40-49	M	Ex	*BABA BBAA* …
3	40-49	M	Never	etc.
4	40-49	F	Current	
5	40-49	F	Ex	
6	40-49	F	Never	
	(etc.)			

Stratified randomization

Advantages

- May prevent bias from chance imbalance between treatment groups on an important baseline prognostic factor.
- Will increase the precision (reduce the variance) of the treatment comparisons made (*increases power*).
- Will facilitate within-stratum (i.e. subgroup) analyses since the treatments will be balanced?
- If important prognostic factors are balanced then the study will be subject to less criticism.

Stratified randomization

Disadvantages

- It is more difficult to implement and therefore more prone to error.
- If quotas are required (requiring a minimum number per stratum), recruitment in some cells may be difficult.

Adaptive randomization

Adaptive procedures change the allocation probabilities as the study progresses.

- Baseline adaptive randomization
  - Biased coin randomization
  - Urn Design
  - Minimization
- Response adaptive randomization
  - Play the winner
  - Two-armed bandit

Who prepares the randomization schedule?

- Randomization should not be prepared by the investigators or clinical staff.
- A “third party” not associated with the day-to-day operations of the trial prepares the randomization.
- The investigators and clinical staff should not have the knowledge of the assignment order.
- Once the assignment order is determined, it should not be changed by the investigators.

Blindness

> A clinical trial should, ideally, have a double-blind design in order to avoid potential problems of **bias** during data collection and assessment. In studies where such a design is impossible, other measures to reduce potential bias are advocated.

Types of trials

1. Unblinded
2. Single-blind
3. Double-blind
4. Triple-blind

Unblinded

- In an unblinded or open trial, both the participant and the investigator know to which intervention the participant has been assigned.
  - Simpler to execute than other studies
  - More accurately reflects clinical practice
- The main disadvantage of an unblinded trial is the possibility of bias.
  - Participant reporting of symptoms and side effects and prescription of concomitant or compensatory treatment are all susceptible to bias.

Examples of unblinded trials

- Comparison of surgical procedures, medical devices
- Changes in lifestyle
- Learning techniques

Single-blind

- In a single-blind study, only the investigator is aware of which intervention each par- ticipant is receiving.
- Simpler to carry out than a double-blind design
- Disadvantages are similar to those for unblinded design

- Both unblinded and single-blind trials are vulnerable to bias by the investigators.
- This relates to group differences in **compensatory** and **concomitant** treatment.
- Investigators may feel that the control group is not being given the same opportunity as the intervention group and, as a result, may prescribe additional treatment as “compensation.”
- Concomitant treatment means any non-study therapy administered to partici- pants during a trial.

Double-blind

- In a double-blind study, neither the participants nor the investigators responsible for following the participants, collecting data, and assessing outcomes should know the identity of the intervention assignment.

Double-blind

Advantages

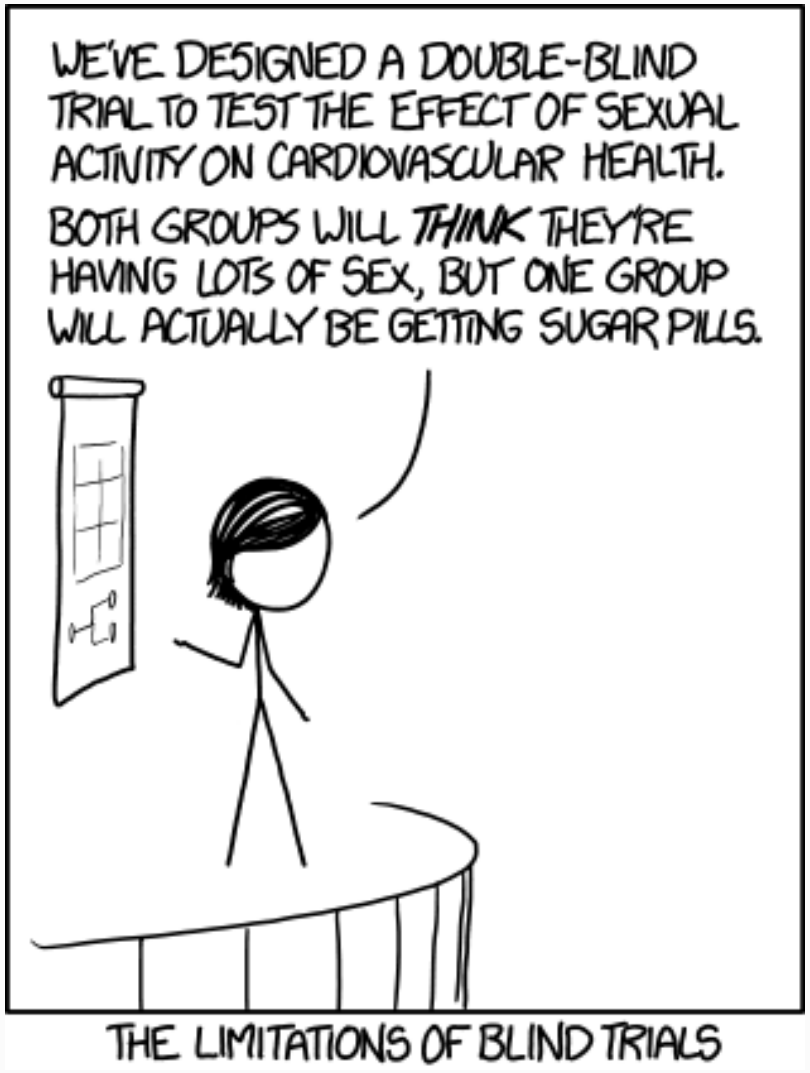
- The risk of bias is reduced.
    - Preconceived ideas of the investigator will be less important because he or she will not know which intervention a particular participant receives.

Disadvantages

- Doesn't protect against imbalances in concomitant medications
- Functions, which could be accomplished by the investigators, must be taken over by others in order to maintain the blindness.

Triple-blind

- A triple-blind study is an extension of the double-blind design.
  - The committee monitoring response variables is not told the identity of the groups.
  - The committee is simply given data for the groups A.
- A triple-blind study has the theoretical advantage of allowing the monitoring committee to evaluate the response variable results more objectively.
- This assumes that appraisal of efficacy and harm, as well as requests for special analyses, may be biased if group identity is known.


WE'VE DESIGNED A DOUBLE-BLIND TRIAL TO TEST THE EFFECT OF SEXUAL ACTIVITY ON CARDIOVASCULAR HEALTH.
BOTH GROUPS WILL THINK THEY'RE HAVING LOTS OF SEX, BUT ONE GROUP WILL ACTUALLY BE GETTING SUGAR PILLS.
THE LIMITATIONS OF BLIND TRIALS