Randomization in RCT

Girmay Medhin

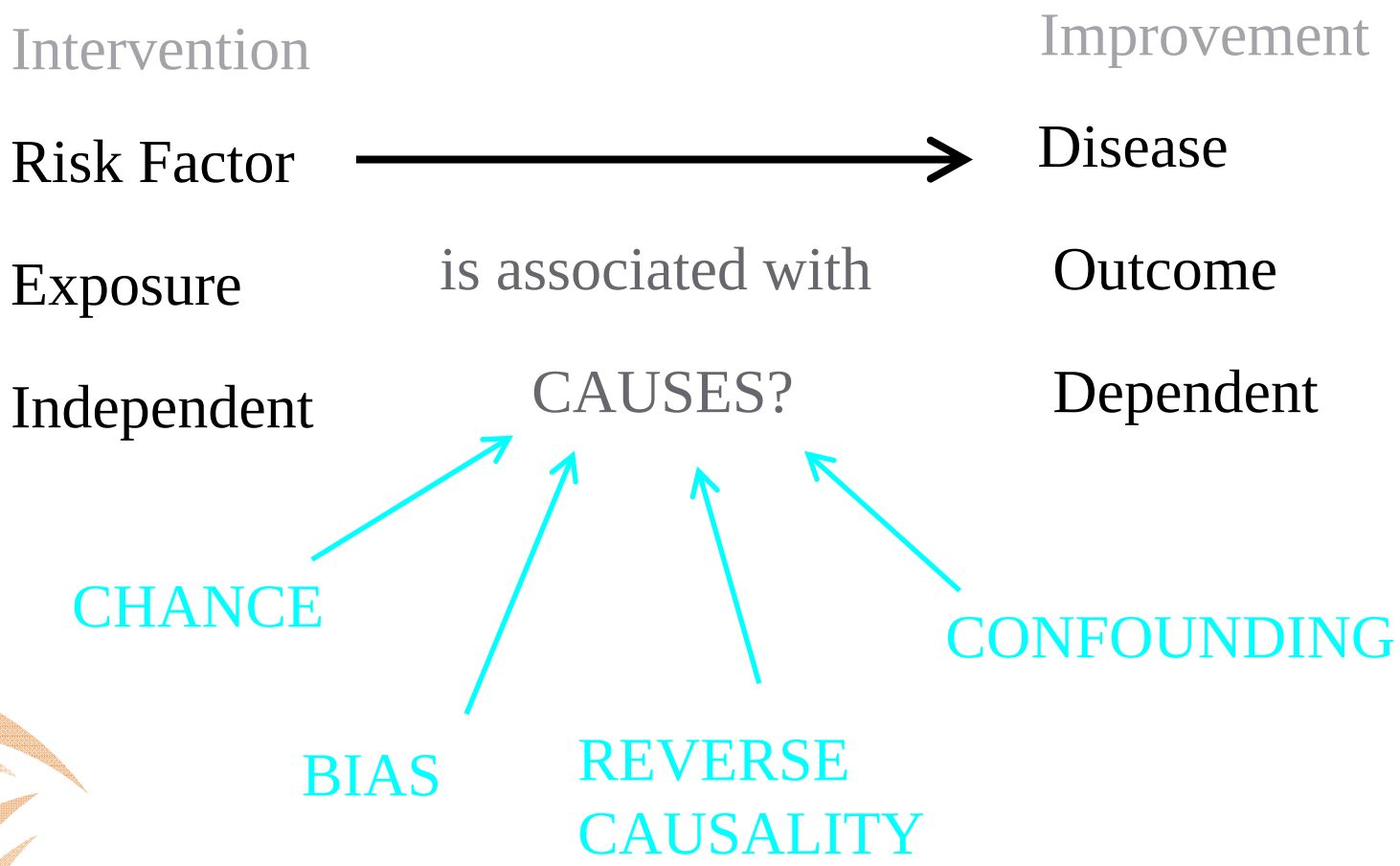
Aklilu Lemma Institute of Pathobiology, AAU

gtmedhin@yahoo.com

Alan J. Flisher Centre for Public Mental Health

AFFIRM
AFrica Focus on Intervention Research for Mental Health

Causation


Intervention
Improvement
Risk Factor
Disease
Exposure
is associated with
Outcome
Independent
CAUSES?
Dependent
CHANCE
CONFOUNDING
BIAS
REVERSE CAUSALITY

What is Randomization?

- A process by which each participant has the same chance of being assigned to either intervention or control

Why do we need it?

- Randomized controlled clinical trial is the standard by which all trials are judged
- Randomization tends to
  - Produce comparable study groups with respect to known as well as unknown risk factors
  - Removes investigator bias in the allocation of participants
  - Guarantees that statistical tests will have valid false positive error rates

Randomization is hoped to take account of

- **Selection bias**
  - Can be minimized by making allocation process not predictable to the investigator and to the study participant

- **Accidental bias**
  - Will be minimal if the procedure achieves balance on risk factors and prognostic covariates

Types of randomization processes

- Fixed allocation randomization
  - Assign the interventions to participants with pre-specified probabilities
  - Allocation probability is not altered as the study progresses

- Adaptive randomization
  - Randomization is progressive
  - Allocation probability is changed as the study progresses
  - One method adjusts the probability of allocation to maintain baseline comparability of the groups
  - Another methods adjusts the allocation probability based on the response of participants to the assigned intervention

Fixed allocation randomization

- Simple randomization
  - Every study participant has equal chance of being allocated to any one of the study arms
  - It is simple to implement
  - Might result in unbalance of treatments in small studies

Fixed allocation randomization

- Simple randomization can be accomplished by
  - tossing unbiased coin each time a participant is eligible to be randomized
  - using random number table with random staring point
    - equally likely digits 0-9 are arranged by rows and columns
  - using a random number producing algorithm
    - participants are assigned to group A with probability p and to group B with probability 1-p
    - for equal probability assignment the cut point is p=0.5
    - p will be different from 0.5 if unequal probability of allocation is needed

Fixed allocation randomization

- Blocked Randomization (permuted block randomization)
  - Used to avoid serious imbalance in the number of participants assigned to each group
  - Participants will be randomized in blocks
  - Number of study participants between groups will be comparable at any stage of randomization

Fixed allocation randomization

- **Example:** Block of size 4 will ensure equal number between two groups after every 4th randomized participants
  - Six possible combinations of group assignment exist
    1. AABB, 2. ABAB, 3. BAAB, 4. BABA, 5. BBAA, 6. ABBA
  - One of these arrangements is selected at random and the four participants are assigned accordingly
  - This step can be repeated as many times as required
  - Mixing of block size (e.g. block sizes of 4 and 6) in a random order minimizes predictability of any allocation)
- How many possible combinations of group assignments do exist in blocks of 2? What about in blocks of 6?

Fixed allocation randomization

- Possible combinations of group assignments in block of 2

  AB, BA

- Possible combinations of group assignments in block of 6

  AAABBB, AABABB, AABBAB, AABBBA

  ABAABB, ABABAB, ABABBA, ABBABA, ABBBAA, ABBAAB

  BAAABB, BAABAB, BAABBA, BABABA, BABBAA, BABAAB

  BBBAAA, BBABAA, BBAABA, BBAAAB,

Fixed allocation randomization

- Stratified Randomization
  - to make the treatment groups comparable in terms of important baseline prognostic factors
    - This could also be addressed during analysis by including the baseline characteristics in the model
  - more important in small studies than in large studies
  - stratifying variables should be measured before or at the time of randomization (Why?)

Fixed allocation randomization

- Stratified Randomization
  - Randomization is done within the target stratum
  - Within each stratum the randomization could be simple or blocked
  - Example: age, sex and history of smoking as stratification variables

Age in years	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

3x2x3 = 18 strata

Baseline Adaptive Randomization

- Biased Coin randomization
  - Randomization into groups with equal probability as long as the number of participants are equal in treatment arms
  - Allocation probability is adjusted if the difference in the number of participants exceed pre-specified number
  - Probability of allocation is higher for the group with fewer participants
  - Investigator decide on the magnitude of the probability
  - Larger probability will correct the imbalance faster

Baseline Adaptive Randomization

- Urn Design
  - This method attempts to keep the number of participants randomized to each group reasonably balanced as the trial progresses
  - Example: Assume a box filled with m red and m black ball.
    - Select one ball at random
    - If the selected ball is red, assign treatment A to the participant and return the ball into the box with one additional black ball
    - If the selected ball is black, assign treatment B to the participant and return the ball into the box with one additional read ball

Response Adaptive Randomization

- Uses information on participant response to intervention during the course of the trial to determine the allocation of the next participant
  - Assign the first participant by the toss of a coin
  - Subsequent participants will only be allocated to anther arm if the response of the previous participant is failure
- Have the intention of maximizing the number of participants on the “superior” intervention
- Developed in response to ethical concerns associated with randomization process
- Meaningful if the outcome is measurable shortly after the intervention

Whose responsibility?

- PI/Sponsor has responsibility of facilitating proper random allocation of eligible study participants into the trail
  - Independent centre or individual might generate the random numbers
    - The allocation code might be delivered to the investigator team by telephone request for every eligible participants
    - The key for trial arms might be kept with independent person and the sequence of allocation codes might be given to a designated member of the investigators
    - The randomization code might also be written on individualized packaging of the intervention
- When should the participant be randomized? Who should allocate him to the trail arm?

Blinding/masking in CRT

Blinding/masking in CRT

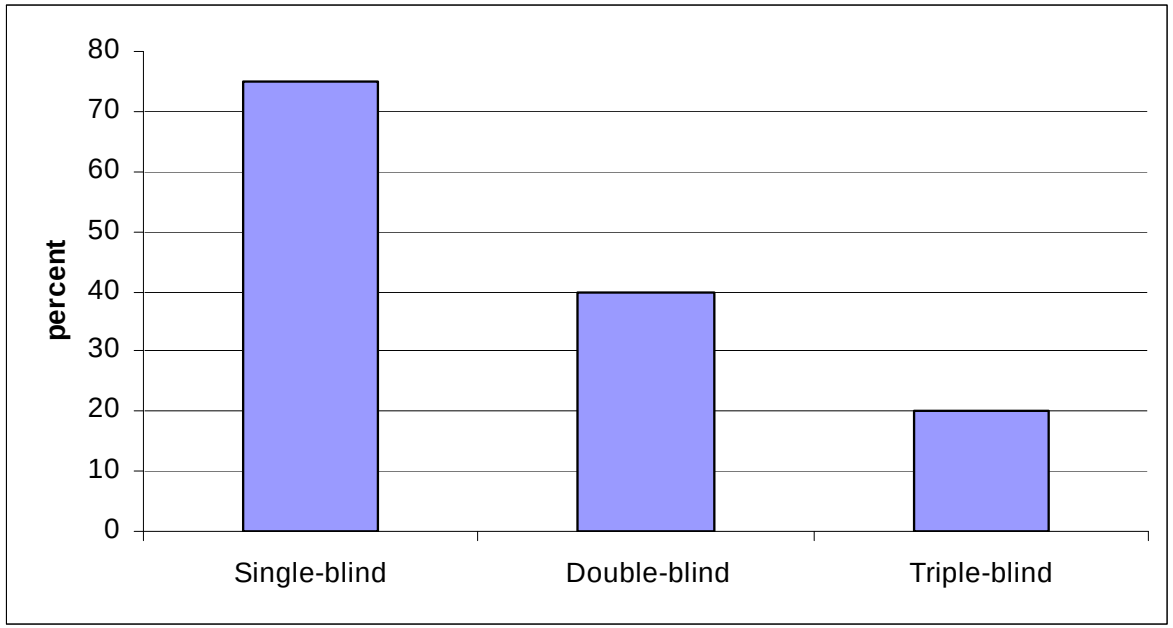
1. **Bias is one of the main concerns in clinical trial**
   - It is a systematic error
   - It is a difference between the true value and that actually obtained due to all causes other than sampling variability

$$\mu_i - \mu = \Delta_i = \gamma_i + \varepsilon_i$$

   - Sampling variability is not a bias
   - Can be caused by
     - Conscious factors
     - Subconscious factors or
     - Both
   - Can occur at any stage of the trial, from the initial design through data analysis and interpretation
   - Can be protected by keeping study participants and investigators masked to the identity of the assigned intervention
   - Large sample size improves precision and power; it does not reduce bias

Blinding/masking in CRT

Physician's correct interpretation of blinding



Devereaux PJ et. al. JAMA 2001; 285:2000-2003

Blinding/masking in CRT

2. Types of clinical trials in terms of masking

- Unblinded/unmasked
  - Study participant and investigator know to which intervention the participant has been assigned
- Single-blind/single-masked
  - Only investigator is aware of which intervention each participant is receiving
- Double-blind/double-masked
  - Neither the participants nor the investigators responsible for following the participants, collecting data, and assessing outcomes should know the identity of the intervention assignment
- Triple-Blind/triple-masked
  - The same as double-blind trial and
  - The committee monitoring response variables is not told the identity of the groups - groups are identified as A and B

Blinding/masking in CRT

2. Advantages and disadvantages of masking

- Unblinded/unmasked
  - Advantage – simplicity, cost , accurately reflects what will happen in practice
  - Disadvantage – prone to bias from investigator and participants
- Single-blind/single-masked
  - Advantage – simplicity, uncompromised participant safety
  - Disadvantage – prone to bias from investigator side
- Double-blind/double-masked
  - Advantage – reduced risk of bias
  - Disadvantage – increased cost and inconvenience
    - treatment allocation and safety monitoring done by independent person implying excessive cost
- Triple-Blind/triple-masked
  - Advantage – the same as double blind; monitoring committee can do their job more objectively
  - Disadvantage – participant safety might be compromised

Blinding/masking in CRT

3. Protecting The Double-Blind Design

- Double-blind studies are more complex
- More difficult to carry out than unblind and single blind trials
  - Investigators should not have access to data which might endanger blindness
  - Effective data monitoring scheme must be set up
  - Emergency unblinding procedures must be established
  - These requirements pose their own problems and can increase the cost of the study
    - Participants want to be on the “better” intervention
    - Investigators might have an interest on positive finding
    - These can be incentives towards unblinding from the participant as well as investigator’s side

Blinding/masking in CRT

3. Protecting The Double-Blind Design

- **Matching of Drugs**
  - Making the trial product and its comparison product as similar as possible
  - Examples of Characteristics for matching
    - Visual (size, shape, color, texture, etc)
    - Packaging (use of identical bottles and vials)
    - Use of double dummy (each active agent has a placebo identical to it and each participant take two medication)
- **Coding of drugs**
  - Labelling of individual drug bottles or vials so that the identity of the drug is not disclosed (e.g. unique random number for each participant)
  - Use of the same code for each study group has an increased risk for unblinding

Blinding/masking in CRT

4. Unblinding

- **Official unblinding**
  - A procedure should be developed to break the blind quickly for any individual participant at any time should it be in his best interest
    - Having a list with the random code and the drug identifier for each participant
    - The list should be with independent person
    - This person should be tractable any time during the trail
    - Potentially, the code could also be placed on individual bottle with precautionary measures in place
    - When unblinding does occur, the investigator should review and report the circumstances which led to it in the results paper

Blinding/masking in CRT

4. **Unblinding**

- **Unintentional unblinding**
  - Occurrence of known pharmaceutical effects of the study medication
  - Full laboratory results might come to the attention of the investigator unintentionally
  - Codes might also come to an investigator in an unexpected ways

Blinding/masking in CRT

5. Assessment and Reporting of Blindness

- In a successfully masked clinical trial
  - Participants and investigators will be masked from the start
  - Masking will be maintained during the conduct of the trial
  - Those assessing trail outcomes will be massed
- Standard operating procedure should be in place to monitor masking of the trial
- During publication of the findings of the trial masking should be reported
  - Who was masked
  - Methodology used to monitor if masking was successful
  - Why and how unblinding was made if there was any
- This will help readers to decide on the level of confidence they should put on the findings of the trial