Randomized Controlled Trial

Training course in research methodology and research protocol development

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GRADUATE ENTRY MEDICAL SCHOOL

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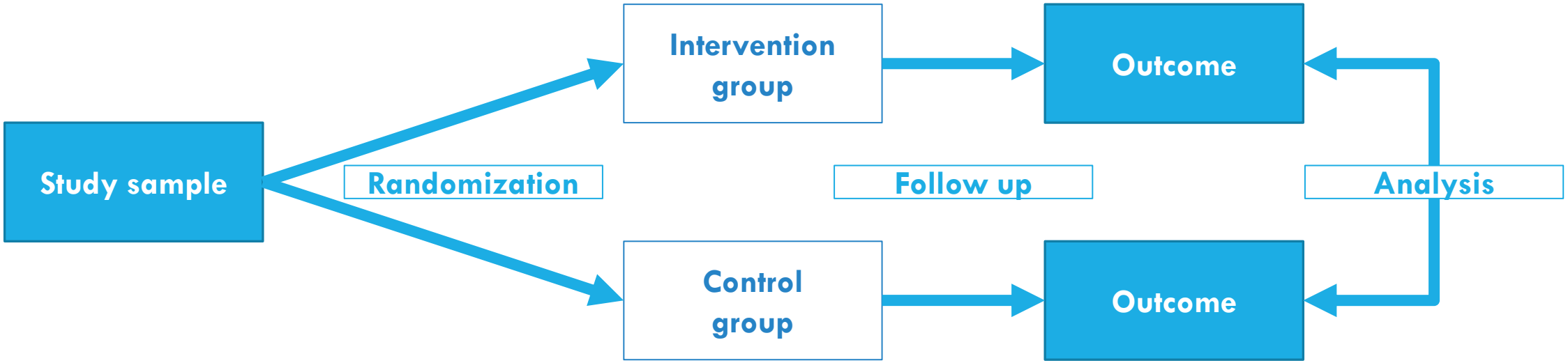
LEARNING OUTCOMES

By the end of the presentation you should be able to:

1. Define randomized control trails, their types, advantages and disadvantages
2. Describe the steps involved in randomization process, blinding, and quality control
3. Discuss methods used to reduce bias in RCT
4. Demonstrate how to register and report RCT
5. Critique a published RCT

RCT
RANDOMIZED CONTROLLED TRIAL

An RCT is conducted to test whether an intervention or treatment works. The investigators will randomly allocate the participants either to the intervention group (which will receive the therapy or preventive action), or to control group (which will receive the usual or no treatment). The two groups are then compared on outcome of interest. Since random assignment equalizes the groups on all other variables, any differences in outcome between treatment and control were actually caused by the treatment.



RANDOMISATION:
STEPS IN A TYPICAL RANDOMISATION PROCESS

1. Sequence generation

- Generate the random allocation sequence by some random procedures
- Participants should be assigned to comparison groups in the trial on the basis of a chance (random) process characterised by unpredictability

2. Allocation concealment

- Develop allocation concealment mechanism (such as numbered, identical bottles or sequentially numbered, sealed, opaque envelopes)

3. Implementation

- Enrol participants
- Assess eligibility
- Discuss the trial
- Obtain informed consent
- Enrol participant in trial
- Ascertain intervention assignment
- Administer intervention

RANDOMISATION: SEQUENCE GENERATION

Type of randomisations		Examples
Simple	Randomization with no constraints to generate an allocation sequence.	*"We generated the two comparison groups using simple randomization, with an equal allocation ratio, by referring to a table of random numbers".*
Restricted	Generate a sequence to ensure particular allocation ratios to the intervention groups	
Blocked	Blocking ensures that the numbers of participants to be assigned to each of the comparison groups will be balanced within blocks of, for example, 5 in one group and 5 in the other for every 10 consecutively entered participants.	*"We used blocked randomization to form the allocation list for the two comparison groups. We used a computer random number generator to select random permuted blocks with a block size of eight and an equal allocation ratio".*
Stratified	Stratified randomisation is achieved by performing a separate randomisation procedure within each of two or more strata of participants (e.g., categories of age or baseline disease severity)	
Minimisation	Minimisation assures similar distribution of selected participant factors between study groups. It incorporates both the general concepts of stratification and restricted randomization	

RANDOMISATION:
ALLOCATION CONCEALMENT

Allocation concealment is the technique of ensuring that implementation of the random allocation sequence occurs without knowledge of which patient will receive which treatment, as knowledge of the next assignment could influence whether a patient is included or excluded based on perceived prognosis.

Ways to ensure concealment:

1. **Central randomization:** In this technique the individual recruiting the patient contacts a central methods center by phone or secure computer after the patient is enrolled.
2. **Sequentially numbered, opaque, sealed envelopes:** The envelopes receive numbers in advance, and are opened sequentially, only after the participant's name is written on the appropriate envelope.

BLINDING

TYPE OF BLINDING

It refers to whether patients, clinicians providing an intervention, people assessing outcomes, and/or data analysts were aware or unaware of the group to which patients were assigned. The goal of blinding is to eliminate, or at least minimize, remaining potential biases.

Single blind: subjects don't know which treatment they are receiving

Double blind: neither subjects nor the investigator who is assessing the patient are aware of the treatment assignment until the end of the study

Triple blind: This term is sometimes used when the person who administers treatment to the study subjects is kept unaware of the assigned treatment.

Quality Control

PROTOCOL ADHERENCE & TREATMENT FIDELITY:

As the independent variable, the treatment plays the lead role in a trial testing whether an intervention works. Procedures need to be in place to ensure that the intervention is implemented as intended

QUALITY MONITORING:

Ongoing quality monitoring is necessary to detect errors and missing data in a timely manner that allows them to be corrected.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Methods need to be in place to identify and report adverse events (AE), or A serious life-threatening adverse event (SAE) that occur during the course of a study.

BIAS:
METHODS TO MINIMIZE BIAS IN RCT

Potential sources of bias	Methods to minimize bias in RCT
Selection bias (biased allocation to comparison groups)	**Randomization** (Generation of allocation sequence and allocation concealment)
Performance bias (unequal provision of care apart from treatment under evaluation)	**Blinding of care providers and patients** Single blind (either subjects or assessors blind) Double blind (both subjects or assessors blind
Detection bias (biased outcome assessment)	**Blinding of outcome assessors** Triple blind (Analysis team is also blind)
Attrition bias (biased occurrence & handling of protocol deviations, withdrawals and losses to follow up)	**Intention-to-treat analysis** (Analysis based on treatment allocation, not adjusted for compliance)

RCT
DIFFERENT TYPES OF RCT DESIGN

There are several variations on the basic RCT design:

Cross-over Design

This describes a special case of a randomized controlled trial wherein each subject serves as his/her own control. In this design, a study is divided into two time periods: During the first time period, each participant receives either the control treatment or the experimental treatment. During the second time period, participants switch conditions. The initial treatment each subject receives is determined by random assignment.

Read this article please http://jamanetwork.com/journals/jamapediatrics/fullarticle/1107589

Cluster randomized design

Whole groups of participants (e.g., schools, clinics, worksites) are randomized to intervention or control. The unit of randomization is a group rather than an individual.

Read this article please http://www.thelancet.com/journals/langlo/article/PIIS2214-109X(15)00287-9/fulltext

RCT:
ADVANTAGES & DISADVANTAGES

Advantages

1. Eliminates selection bias, balancing both known and unknown prognostic factors by distributing confounders equally between the groups to be compared for the outcome.
2. Random assignment permits the use of probability theory to express the likelihood that any difference in outcome between intervention groups merely reflects chance
3. Facilitates blinding the identity of treatments to the investigators, participants, and evaluators which reduces bias after assignment of treatments

Disadvantages

1. Expensive in terms of time, personnel and resources
2. Ethical issues for certain interventions or circumstances
3. May be unsuitable because of problems of likely co-operation or rarity of outcome
4. Tend to induce artificial situation because of
   - Volunteerism
   - Strict eligibility criteria
   - Highly standardised interventions that may be different from occurs in common practice (difference between efficacy and effectiveness)

REPORTING RCT
CONSOLIDATED STANDARDS OF REPORTING TRIALS

The CONSORT provides a set of standards for reporting the results of randomised controlled trials (RCTs)

It encompasses various initiatives to alleviate the problems arising from inadequate reporting of randomized controlled trials.

It is main product is the CONSORT Statement, which is an evidence-based, minimum set of recommendations for reporting randomized trials. It offers a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.

CONSORT

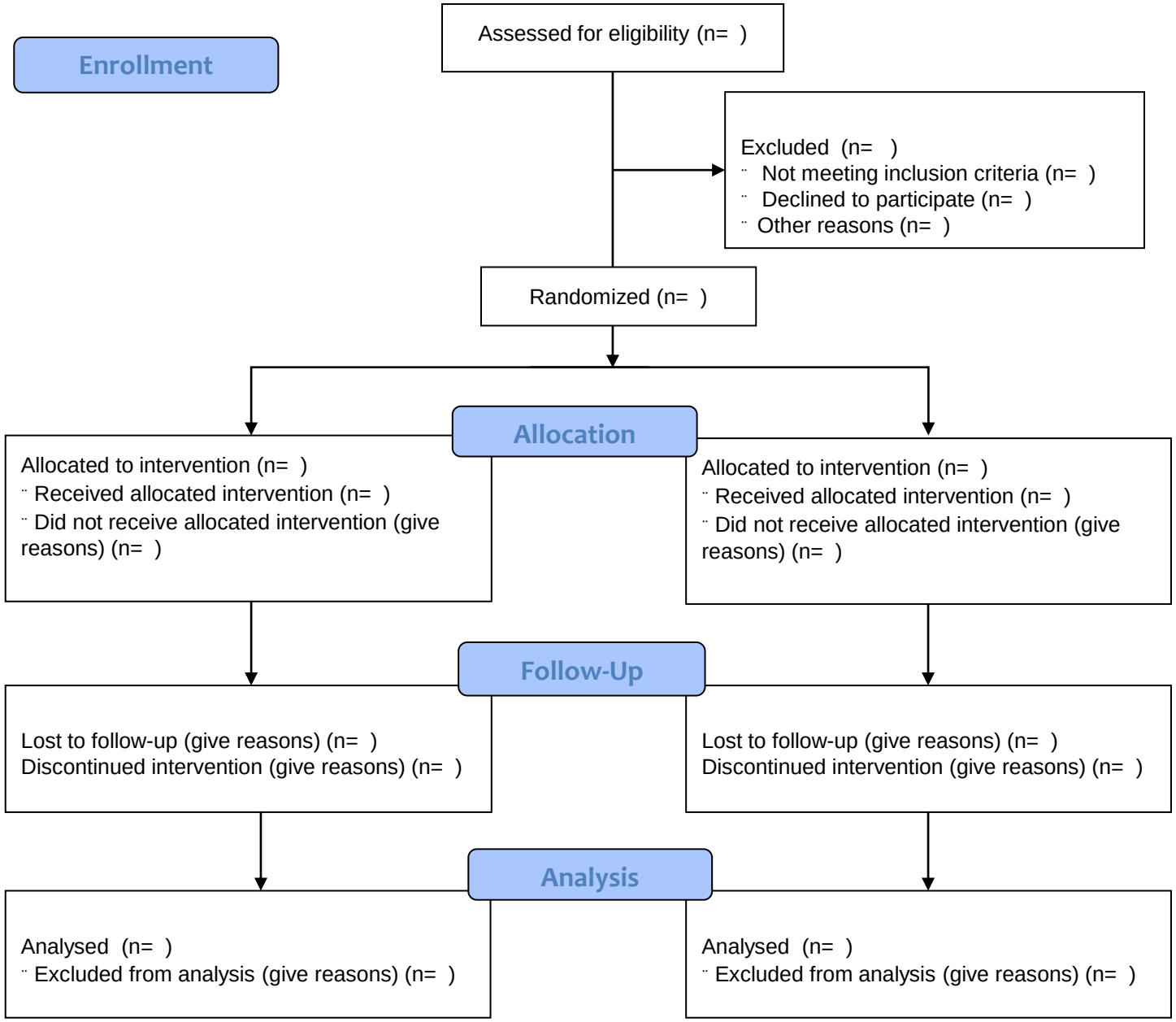
CONSORT

TRANSPARENT REPORTING of TRIALS

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram

[Click here to download the flow diagram]



CONSORT 2010 checklist of information to include when reporting a randomised trial

Click here to download the checklist

Section/Topic	Item No	Checklist item	Reported on page No
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	
Participants	4a	Eligibility criteria for participants	
	4b	Settings and locations where the data were collected	
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined	
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	

REGISTERING RCT
INTERNATIONAL CLINICAL TRIALS REGISTRY PLATFORM

Trial registration: The registration of all interventional trials is a scientific, ethical and moral responsibility.

The mission of the WHO ICTRP is to ensure that a complete view of research is accessible to all those involved in health care decision making. This will improve research transparency and will ultimately strengthen the validity and value of the scientific evidence base.

WHO regards trial registration as the publication of an internationally-agreed set of information about the design, conduct and administration of clinical trials. These details are published on a publicly-accessible website managed by a registry conforming to WHO standards.

Where to register a trial?

Details of RCTs should be submitted to any one of the Primary Registries in the WHO Regis Network

EXAMPLE

Click on the link to read the article. Read this article and use CONSORT checklist to verify its quality

Please click here to read this article

GLOSSARY

Allocation concealment	A technique used to prevent selection bias by concealing the allocation sequence from those assigning participants to intervention groups, until the moment of assignment. Allocation concealment prevents researchers from (unconsciously or otherwise) influencing which participants are assigned to a given intervention group.
Allocation ratio	The ratio of intended numbers of participants in each of the comparison groups. For two group trials, the allocation ratio is usually 1:1, but unequal allocation (such as 1:2) is sometimes used.
Allocation sequence	A list of intervention groups, randomly ordered, used to assign sequentially enrolled participants to intervention groups. Also termed the "assignment schedule", "randomization schedule", or "randomization list".
Blinding (masking) -	The practice of keeping the trial participants, care providers, those collecting data, and sometimes even those analyzing data unaware of which intervention is being administered to which participant. Blinding is intended to prevent bias on the part of study personnel. The most common application is "double-blinding", in which participants, caregivers and those assessing outcome are blinded to intervention assignment. The term "masking" may be used instead of blinding.
Enrollment	The act of admitting a participant into a trial. Participants should be enrolled only after study personnel have confirmed that all the eligibility criteria have been met. Formal enrollment must occur before randomized assignment
Follow-up	A process of periodic contact with participants enrolled in the randomized trial for the purpose of administering the assigned intervention(s), modifying the course of intervention(s), observing the effects of the intervention(s), or for data collection.
Generation of allocation sequence -	The procedure used to obtain the (random) sequence for making intervention assignments, such as use of a table of random numbers or a computerized random-number generator. Options such as simple randomization, blocked randomization, and stratified randomization are part of the generation of the allocation sequence.
Intention-to-treat analysis	A strategy for analyzing data in which all participants are included in the group to which they were assigned, whether or not they completed the intervention given to the group. Intention-to-treat analysis prevents bias caused by the loss of participants, which may disrupt the baseline equivalence established by random assignment and which may reflect non-adherence to the protocol.

GLOSSARY

Outcome (primary and secondary)	An outcome variable of interest in the trial (also called an end point). Differences between groups in the outcome variable(s) are believed to be the result of the differing interventions. The primary outcome is the outcome of greatest importance. Data on secondary outcomes are used to evaluate additional effects of the intervention.
Performance bias	Systematic differences in the care provided to the participants in the comparison groups other than the intervention under investigation.
Permuted block design	An approach to generating an allocation sequence in which the number of assignments to intervention groups satisfies a specified allocation ratio (such as 1:1 or 2:1) after every "block" of specified size. For example, a block of size 12 would contain 6 A and 6 B with a ratio of 1:1 or 8 A and 4 B with a ratio of 2:1. Generating the allocation sequence involves randomly selecting from all the permutations of assignments that meet the specified ratio.
Prognostic variable	A baseline variable that is prognostic in the absence of intervention Unrestricted, simple randomization can lead to chance baseline imbalance in prognostic variables, which can affect the results and weaken the trial's credibility. Stratification and minimization protect against such imbalances.
Selection bias	Systematic error in creating intervention groups, such that they differ with respect to prognosis. That is, the groups differ in measured or unmeasured baseline characteristics because of the way participants were selected or assigned. Also used to mean that the participants are not representative of the population of all possible participants.
Loss to follow-up	The circumstance that occurs when researchers lose contact with some participants and thus cannot complete planned data collection efforts. A common cause of missing data, especially in long-term studies.
Bias	Systematic distortion of the estimated intervention effect away from the "truth", caused by inadequacies in the design, conduct, or analysis of a trial.

READING MATERIALS & USEFUL LINKS

CONSORT http://www.consort-statement.org/

WHO ICTRP http://www.who.int/ictrp/en/

ClinicalTrials.gov https://www.clinicaltrials.gov/ct2/home

Trials journal https://trialsjournal.biomedcentral.com/

The SPIRIT Statement: http://www.spirit-statement.org/spirit-statement/

Get Certified in Clinical Research :

The Association of Clinical Research Professionals (ACRP)

https://www.acrpnet.org/certifications/