Experimental Studies

Objectives:

1. **To lean about types of experimental design**

Team Members:

khalid aleedan - khalid alhusainan - mohammad ghandour – Munirah Aldofyan

Team Leaders: Mohammed ALYousef & Rawan Alwadee

Revised By: Yara AlDigi & Maha AlGhamdi

Resources:

• 436 Lecture Slides + Notes

Important – Notes

436researchteam@gmail.com

Editing file

Feedback link

EXPERIMENTAL STUDIES

All experimental studies are prospective

TRUE EXPERIMENTS

-RANDOMIZED TRIALS" GOLD STANDARD"

Types

Phase | : on healthy human
Phase || on patients to determine best dose
Phase |||: to establish efficacy
Phase |||b : drug has markting authorization but indication is expanded
Phase iv : post registration studies

Disadvantages

1. Costly (time, money)
2. May not be suitable for some research questions
a. ethical barriers b. outcomes rare
3. Generalizability (standardized interventions, follow-up, inclusion/exclusion criteria

Advantages

Strongest evidence for cause and effect

Designs

- Parallel
- Factorial
- Cross-over

QUASI-EXPERIMENTS

1-Cross-sectional comparison:
2-Temporal comparison
3-Combinations of the above

Assessing the Validity of a Clinical Trial

1. Randomization 2. Allocation concealment 3. Blinding 4. Loss to follow-up

Quantitative Study
Designs

- **Intervention:** True experiment (RCT)
- **Analytic:** Case-control, cohort.
- **Descriptive:** Case studies, Case series, Ecological studies, Cross-sectional, Surveys.

Types of experimental studies:

1. True experiments -randomized trials
2. Quasi-experiments " Non randomized trails " لان انا اختار المجموعة الي ابي اسوي عليها التجربه واقارنها قبل وبعد

The difference between RCT and QUASI, is that the allocation in QUASI is not random

Randomized Controlled Trials: Randomized clinical trials is a gold standard why ? Because of temporality , we move forward "you sure this cause this "

- Randomized Clinical Trial (RCT) is gold standard
- RCT minimizes bias
- Can't do RCTs for all important questions (time, funding, ethics)
- Must make choices on what evidence to use for clinical guidelines

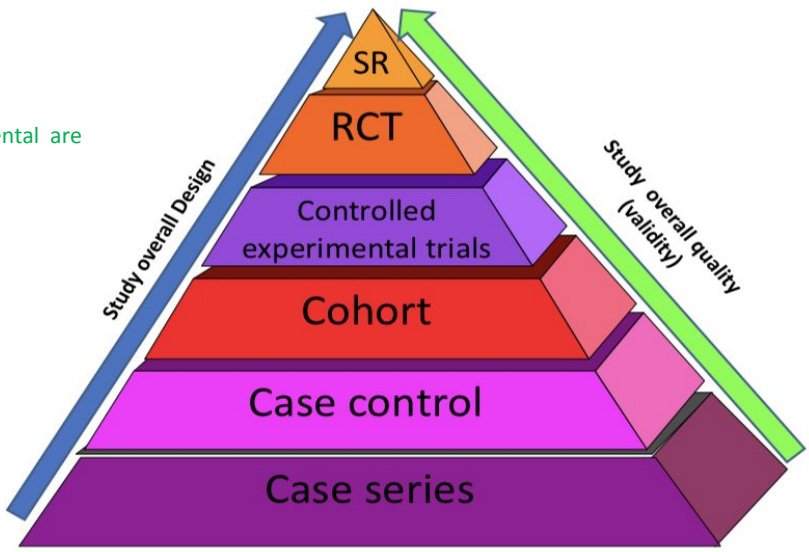
Intervention

1. New drugs and new treatment of diseases
2. New medical and health care technology
3. New methods of primary prevention
4. New programs for screening
5. New ways of organizing and delivering health services
6. New community health programs
7. New behavioral intervention program

QUASI-EXPERIMENTS (NON RANDOMIZED)

1-Cross-sectional comparison:
comparable communities or groups
2- Temporal comparison:
before and after the intervention
3- Combinations of the above:time-series analysis in community trial.

cohort and experimental are **prospective**



Prospective evaluation

- **What is a prospective evaluation?**
  - Evaluation designed in advance
- **Advantages**
  - Collect specific data
  - Collaborative design and evaluation
- **Disadvantages?**
  - Long term results emerge in the long run
  - Q: What approaches could give us long run results in the short run?

Comparator in experimental study:

- Therapy vs. no therapy — Such as giving specific group of people drug X and other group are not taken the drug . (ASPIRIN VS NO ASPIRIN)
- Therapy vs. placebo or sham — مثلا اعرض بعض الناس لدواء معين واجيب ناس اخرين وأقنعهم ان هذا هو الداء نفسه ولاكن هو بلاسيبو واشوف النتيجة
- Therapy A vs. Therapy B

RCT Advantages:

- Strongest evidence for cause and effect " temporality I'm sure exposure to this will lead to this outcome "

RCT Disadvantages:

1-Costly (time, money)

2-May not be suitable for some research questions

- ethical barrier
- outcomes rare ex. Cancer would need a cohort study since it'll take a longer time but you can randomize cancer patients to therapy to see how they'll become in a year or two.

3-Generalizability (standardized interventions, follow-up, inclusion/exclusion criteria) like if you want to try a drug for treating a cancer but you dont have paitents with specific charactrastics

Types of RCT:

Randomized Clinical Trial

phase I	the first studies carried out in humans.
phase II	studies carried out in patients, usually to find the best dose of drug and to investigate safety
phase III	pivotal RCTs (usually 2) to establish efficacy. Typically these are the studies on which registration of a new product will be based.
phase IIIb	when a product already has marketing authorization but the indication is being expanded.
phase IV	post registration studies. Usually for marketing purposes, also to gain broader experience with using the new product.

Phase I

In healthy human – very small number 10-12 – to test side effects – tolerance and major toxicity – "used in human in small dose to test its safety"

Treatment mechanism(s)

Uptake, distribution & elimination

Fibonacci Dose Escalation

Conservative starting dose (10% of LD_{10})

1, 1, 2, 3, 5, 8, 13, 21, …

Groups of 3

Continue until 2 of 6 experience toxicity

Mild disease / normal volunteers (n= 20 to 80)

used on healthy (humans) in small sizes (10-12) and small dose

Phase II

Here we can judge which dose are effective in treatment

- Fixed dose → determine of Tx should be used in a large scale comparative trial
- Feasibility: side effects, toxicity, logistics of administration & cost
- Efficacy: surrogates
- Toxicity, side effects & benefits.
- Randomized SE studies (parallel / x-over)
- Sample size: 50 to 200 patients

Dose finding phase هذي المرحلة اسمها
يعني نزود جرعة الاسبرين الين مايوصل ل dose معينة علشان يسوي inhibition for the platelate
so once we reach to a dose that inibits tha platelat its called dose finding - يعني اشوف الجرعة كيف تناسب الجسم

Phase III

عيبها هنا - Large trail
الجنيرااليزابيلتي فلو حتى نزل الدواء في السوق يحتاج مراقبه لان فئه اكبر راح تجربه

Determine efficacy vs. standard therapy

Compare incidence and severity of side effects vs. standard therapy

- Single therapy
- Combined therapies (cancer)

Often multi-centre

- Logistics
- Heterogeneity

Phase IV

here you want to see two things

1- validation and the effecacy of a drug
2- assures that are no side effects

Longer term data

- Approval based on small numbers or relatively brief follow-up

Impact of therapy when applied to large / diverse populations

Large sample size (rare outcomes)

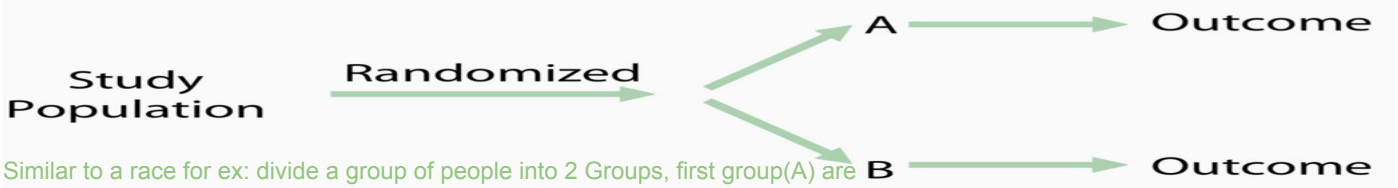
Challenge: impact of therapy vs. course of disease or other factors

Designs of RCT:

RCT:

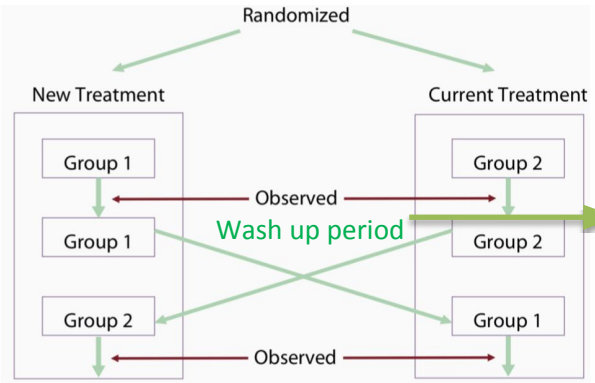
- Parallel (practical)
- Factorial
- Cross-over
- Pragmatic
- Adaptive (changing)

Parallel:



Similar to a race for ex: divide a group of people into 2 Groups, first group(A) are taking Aspirin and the other group(B) are taking a placebo, then we'll check how many develop an MI in each group. (we'll follow them up for 1-2 years)

cross – over:



If for example 12 develop an MI while using Aspirin, and 25 develop an MI while using the placebo then taking an Aspirin will decrease the chance of getting an MI by 50%

-after 6 month we switch between aspirin and placebo
this is called cross-over. If you're using devices then you'd switch them off/on depending on how the subject started. (if the device was on you'd turn it off and if the device was off you'd turn it on)

: the period in which the old drug element from the body , So you have to wait before switching the drug .

The point of a cross-over study is to have a comparison within one person (since he has used bothe the placebo and drug)

Factorial:

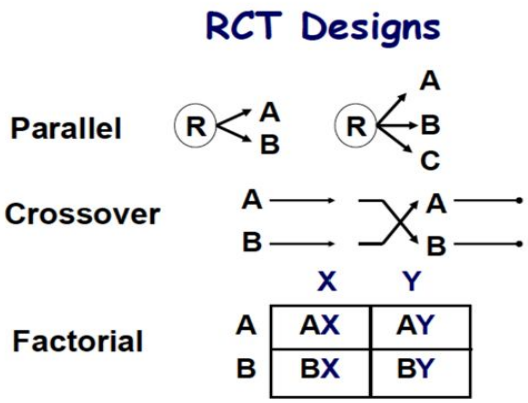
Treatment A	Treatment B +	Treatment B −
+	Both A and B	A only
−	B only	Neither A nor B

In factorial for example we want to compare between Aspirin and Omega-3 on preventing death
so we can divide it into 2X2 table
Group 1 - Take Aspirin only
Group 2 - Take Omega-3 only
Group 3 - Take both
Group 4 - Take neither Aspirin nor Omega -3 they will have placebo

Allowing us to answer 3 questions:
1- what is the effect of omega 3 on mortality vs the placebo?
2- what is the effect of aspirin on mortality vs the placebo?
3-what is the synergis effect of both on mortality vs the placebo?
(the placebo group will function as the control group)

Factorial Design:

- **Advantages:**
  1. Two studies for one
  2. Discover interactions
- **Disadvantages:**
  1. Test of main effect assumes no interaction
  2. Often inadequate power to test for interaction
  3. Compliance
- **Examples:**
  - Physicians' Health Study (PHS) NEJM 321(3):129-135, 1989.
  - Final report on the aspirin component
  - Canadian Cooperative Stroke Study (1978) NEJM p. 53



Considerations in Assessing the Validity of a Clinical Trial:

1. Randomization (very important)
2. Allocation concealment
3. Blinding
4. Loss to follow-up

they all should be valid otherwise if one of them fail the clinical trial drops down to prevet Bias

Randomization: So you will have an equal chance of being from either group A or B

- **Randomization:** is the process by which allocation of subjects to treatment groups is done by chance, without the ability to predict who is in what group So you will have equal chance either in group A or group B
- **Primary purpose**
  - Prevent bias in allocating subjects to treatment groups (avoid predictability)
- **Secondary purpose**
  - Achieve comparability between the groups (there is no guarantee)
- All patients have the same chance of receiving either treatment or control
- Sequence of allocation to treatment or control must be unpredictable
- Helps ensure that the treatment and control groups will have similar characteristics
  - Both known and unknown factors are equalized
- Avoids selection bias
  - Sometimes called “confounding by indication”

Allocation Concealment:

- The investigator entering a patient into the study should not know if the patient will be assigned to treatment or control
  - They might try to put the sicker patients into the control group to make the treatment look good
  - They might try to put the sicker patients into the treatment if they believe the treatment is effective
- Can be prevented by using a telephone service or computer for randomization

for example I have alot of boxs half with drug and the other half with placebo me as a doctor i shoud not now which is which , there will be a person who knowe the code for each box

Concealed allocation:

- Concealed allocation is an extension of randomization
- When obtaining informed consent to enroll a patient into a trial, the investigator does not know if the next patient will get new treatment or control
- RCT comparing new therapy vs. placebo for abdominal pain in irritable bowel syndrome
- Investigator interviews the next eligible patient, who complains of long-term severe, unrelenting symptoms that have never responded to previous medical therapy
- Next patient to enter trial will get placebo
- Investigator thinks that placebo is unlikely to relieve abdominal pain in this patient
  - Investigator may subconsciously try to convince patient not to enroll in the trial
- Consequence: patients with severe abdominal pain will NOT be evenly divided between new therapy and placebo groups

Blinding:

• **Masking or blinding** is used to increase the objectivity of the persons dealing with the randomized study (to prevent prejudice)

• Subjects who can be masked/blinded
  − Study participants
  − Caregivers/treaters
  − Data collectors/assessors of outcome − Data analysts

• − Investigators
  Level of masking/blinding

• − Non-blinded (open)
  − Single
  − Double
  − Triple

• **Single blinded:** patient doesn't know which arm any patient is in.

• **Double blinded:** patient and person administering the intervention don't know.

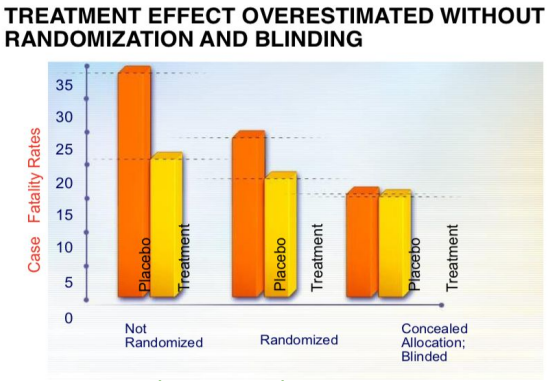
• **Triple blinded:** patient, interventionist and data analyst don't know.

• Also referred to as "**masking**"

• Blinding of the investigators prevents ascertainment bias
  • Data collectors
  • Outcome adjudicators
  • Data analysts

• Blinding of patients equalizes the placebo effect

• Blinding of caregivers prevents unequal treatment



Concealed allocation is done before the administering of the drug whereas blinding

Double blinding ex, if the drug used is to reduce bleeding the physician could omit drug, however if he doesn't know then he'll feel obliged to report everything that has happened.

Loss to follow-up: It can affect the outcome

• Participants may leave a study for a variety of reasons
  ▪ moving out of town
  ▪ too burdensome to comply with the study protocol
  ▪ experiencing adverse effects from the intervention
  ▪ feeling well or cured by the intervention
  ▪ death

• How to deal with lost participants
  ▪ find out why the were lost
  ▪ assume the worst, and see how it affects results

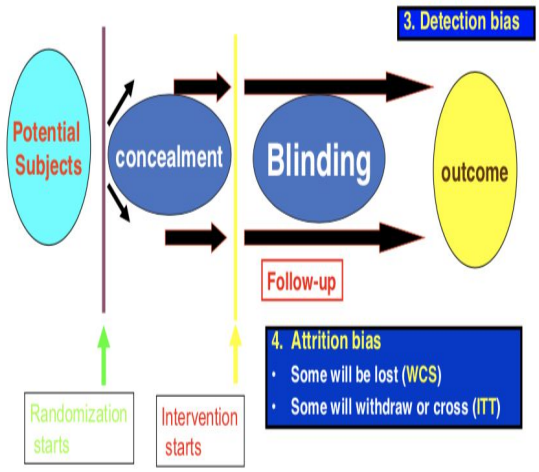
If you assumed the worst case scenario and the active drug is better than you've done a good trial.

Compliance:

• **Compliance** is the willingness of the participants to carry out the procedures according to the established protocols (adherence)

• **Drop-outs** are the participants who do not adhere to the experimental regimen during follow-up

• **Drop-ins** are the participants who do not adhere to the control regimen during follow-up



Analysis:

• Primary: **intention to treat**
  − Analyze according to original allocation
  − Net effect of non-compliance is to reduce the observed differences

• Secondary: actual treatment received − Based on observed data − No benefit of randomization

THE END