
MEDICAL RESEARCH
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الدكتور: منير أبو هلالة

Overview of study designs

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Color code

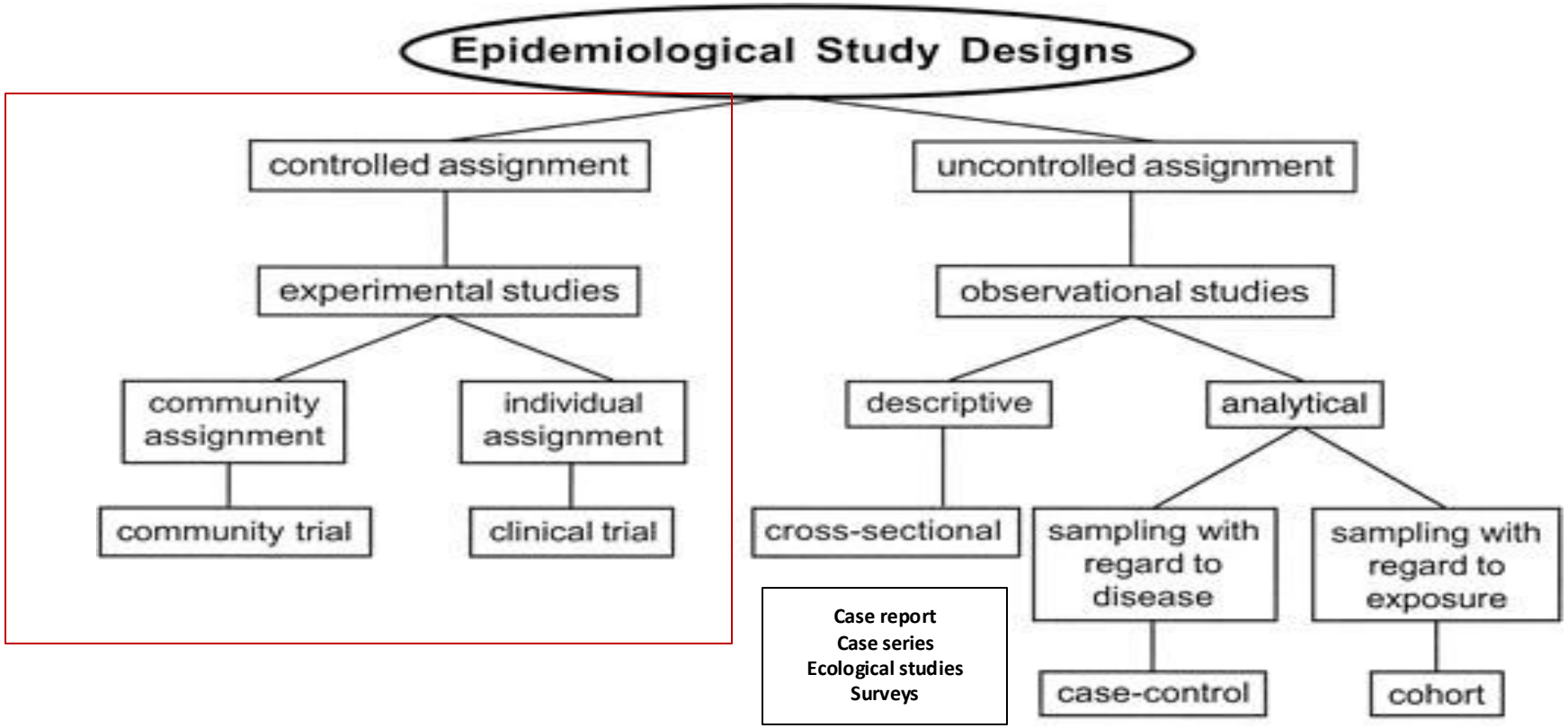
- Slides
- Doctor
- Additional info
- Important

- بسم الله الرحمن الرحيم

- When we have different cross-sectional studies looking at, for example, the prevalence of hypothyroidism in different countries and we want to have just one figure related to the global prevalence of hypothyroidism, we can combine these different studies together using what we call the **meta-analysis technique**. This allows us to come up with an overall prevalence of 5%, 10%, or 3% worldwide. Again, we are **combining data** from different individual studies to produce one summary estimate of the overall effect. This is what we call **meta-analysis**.

- In meta-analysis, we combine the results. However, in **systematic reviews**, we **can't combine** the results. ChatGPT states that in both methods—systematic review and meta-analysis—we can combine the results, but the doctor explains the distinction as follows:
- If we have different clinical trials conducted on treatment X for the treatment of type 2 diabetes, and we observe these clinical trials conducted over the last three years, we can combine these clinical trials into one finding when there is no heterogeneity between the studies. This results in a single outcome that shows the combined result, and this is referred to as **meta-analysis**.
- However, if there is heterogeneity between these studies and we cannot combine them, we present the results separately, perhaps in one table or two tables, and this is referred to as a **systematic review**.

- **The highest level of evidence** in medical research or evidence-based medicine comes from **meta-analysis and systematic reviews**, followed by clinical trials. Combining different clinical trials together into one unit makes the evidence stronger than a single clinical trial, which is the essence of meta-analysis.
- Check the last slide for external sources recommended by the doctor



Source: Waning B, Montagne M: *Pharmacoepidemiology: Principles and Practice*: http://www.accesspharmacy.com

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We classify studies into controlled assignment and uncontrolled assignment:

1. **Uncontrolled assignment**: it is just an observational study, we **don't have any intervention.**
2. **Controlled assignment**:As an investigator, you will have an impact—you control something, change something, or **perform an intervention**. Examples include:
   - Giving Group A treatment X and Group B the standard treatment or a placebo. (Placebo is an inactive substance or treatment that lacks any therapeutic effect, such as sugar pills or saline injections.)
   - Comparing open surgery versus laparoscopic surgery.
   - compare general practitioners with family physicians to see the impact of management of newly diagnosedd diabetic patients after one year, **firstly**, **I randomized** these newly diagnosed patients with type 2 diabetes to be seen by family physician or general practitioner. After one year I'll compare the HbA1C for example as a marker for the glycemic control, I compare General practitioners with family physician.
   - Comparing patients on the same medication but with different doses, or comparing different treatments (e.g., treatment A versus treatment B, early referral versus late referral).

- In experimental studies under controlled assignment, we further classify studies into two types:

1. Community assignment
2. Individual assignment

Individual Assignment:	Community Assignment
In this type, we compare one **person** to another (e.g., clinical trials or preventive trials).	Here, we compare **groups** of people rather than individuals.
we have **clinical trial, preventive trial**, I'll give the patient this treatment and the other patient the standard placebo or treatment هون بنقارن بين شخص و شخص Example: To assess the impact of early referral physiotherapy for patients with severe low back pain: Group A (Arm A): Patients receive early physiotherapy and are seen within 48 hours. Group B (Arm B): Patients receive the standard referral physiotherapy. After six weeks, you assess outcomes such as quality of life or pain scale to compare early referral with standard referral.	Example 1:To improve medical students' research participation:At Jordan University, you give online lectures at the start of the first term and assess the number of studies conducted by students at the end of the year.At Jordan University of Science and Technology, you provide only leaflets or posters about the importance of research.You compare these two interventions to evaluate their effectiveness.احنا هون بنقارن بين مجموعة طالب ومجموعة طالب ثانية Example 2:To study interventions for smoking cessation among teenagers:In Mafraq, secondary school students receive lectures and seminars about smoking.In Irbid, secondary school students are given posters and leaflets about smoking.You compare smoking prevalence at the start and end of the one-year intervention program to determine the relative effectiveness of the approaches. Example 3:To reduce dental caries in children under the age of five:In Aqaba, fluoride levels in the water supply are increased within an acceptable limit, and the incidence of dental caries is assessed over three to five years.In Karak, fluoride levels remain within normal status (without any increase).You compare the incidence of dental caries in Aqaba and Karak to evaluate the impact of increasing fluoride in water.(Note: Increasing fluoride levels within acceptable limits reduces dental caries.)

Experimental Study Design

- A study in which a population is selected for a planned trial of a regimen, whose effects are measured by comparing the outcome of the regimen in the experimental group versus the outcome of another regimen in the control group.

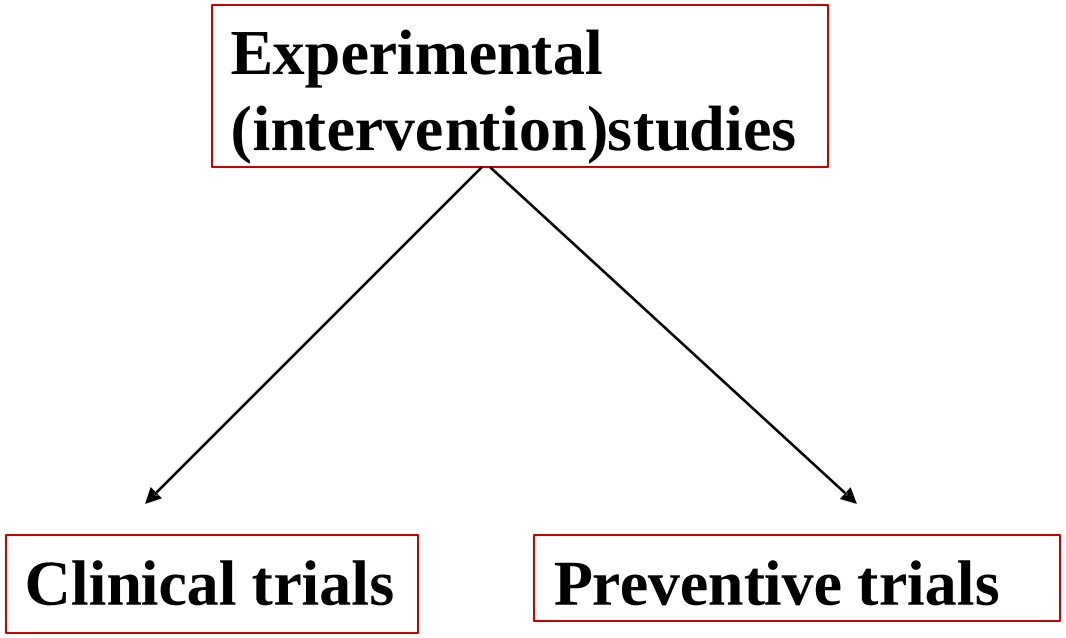
(**control group** : group **not** exposed the intervention or the experimental treatment) ركز شوي

When conducting a clinical trial, if there is an existing treatment for a condition (e.g., hypertension) and you have developed a new, potentially better intervention to control blood pressure, the appropriate comparison should be made between the **new intervention** and the **existing treatment.**

However, if you are dealing with a disease that has no cure or no existing treatment, then it is acceptable to compare the **new intervention** with a **placebo**.

This ensures ethical standards and proper evaluation of the effectiveness of the new intervention.

Experimental studies (Intervention)



Clinical trials and preventive trials are two types of experimental studies, each serving distinct purposes:

1. **Clinical Trials:**

In clinical trials, the primary aim is to **cure** a disease or to **control** its progression.
For example, you provide treatments for conditions like hypertension, diabetes, or cancer to manage or eliminate the disease.

2. **Preventive Trials**:

Preventive trials focus on **preventing** / stop the **occurrence** or **recurrence** of a condition.
Examples include:Administering aspirin to prevent the recurrence of myocardial infarction (MI).Providing vaccines to healthy pediatric populations to prevent infections.

Experimental Study Design

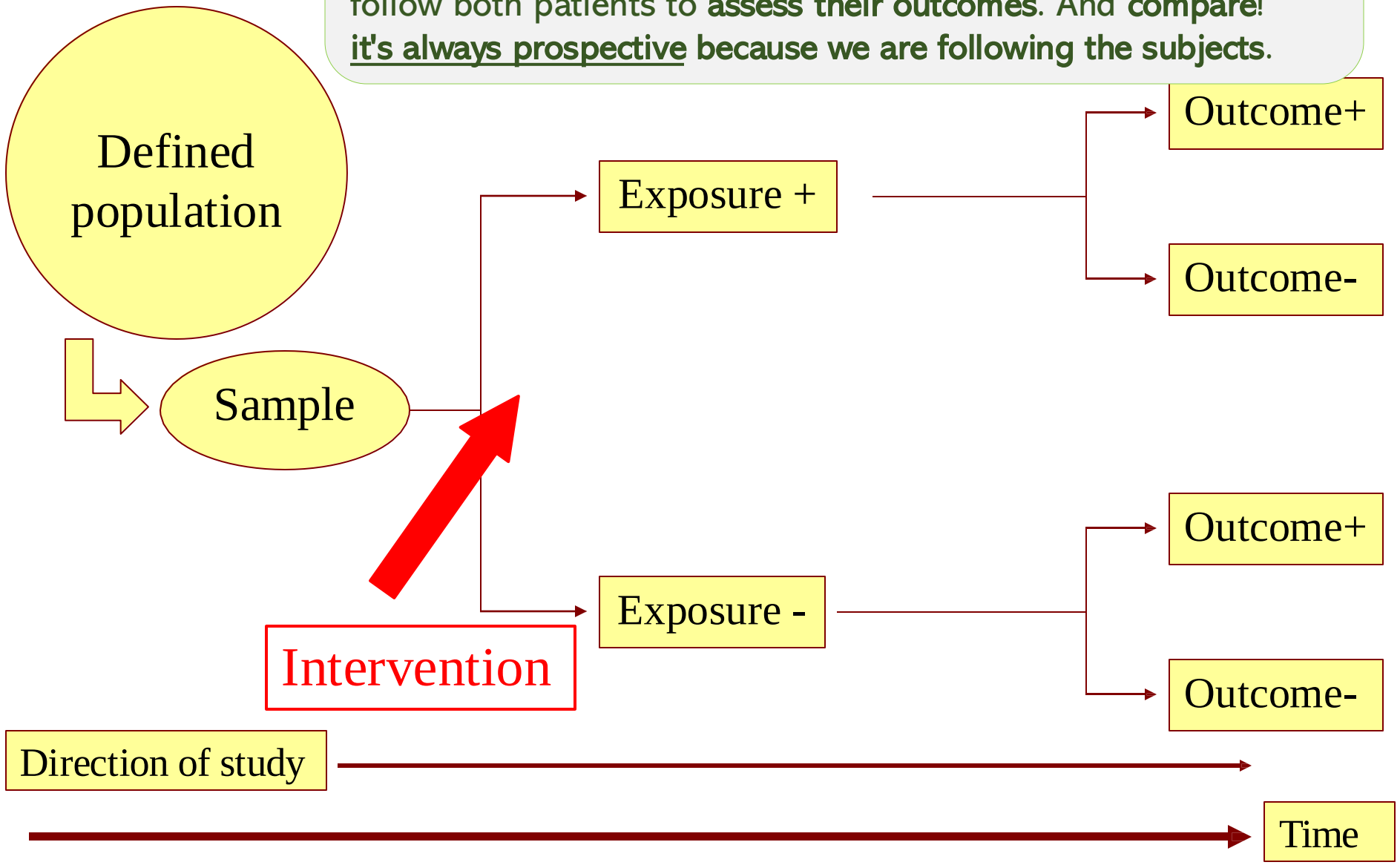
- Different from observational designs by the fact that there is manipulation of the study factor (exposure), and randomization (random allocation) of subjects to treatment (exposure) groups.

Experimental studies, unlike observational designs, involve active intervention.
In these studies:
We do something:This could include giving aspirin, administering a treatment, or implementing an intervention. **introduce exposure**

We perform random allocation: Subjects are randomly assigned to different groups, such as treatment A or treatment B. This ensures that each subject in the study has an equal chance of being placed in any of the groups, reducing bias and enhancing the reliability of the results.

Clinical trial

Small diagram shows you how in clinical trial we try a new treatment(intervention) to cure a disease by exposing some patients to the new treatment and some without it, then we follow both patients to **assess their outcomes**. And **compare**! **it's always prospective because we are following the subjects**.



Why experimental study design?

- Limitations of theory
- Previous disasters

Clofibrate: Check the next slide

Successfully lowers cholesterol

Treated group: reduced CHD incidence, but higher all causes mortality

- Spontaneous improvements
- Importance of small effects

- **Experimental studies** are essential to demonstrate the impact of different interventions. Without a control group or a clinical trial, we may fail to detect serious adverse reactions.

- Example

Consider Clofibrate, a drug proven to successfully lower cholesterol levels.

In a study, Clofibrate was administered to one arm (one group of subjects), and some mortality was observed in this group.Initially, researchers attributed the mortality to unknown causes or reasons unrelated to Clofibrate.

However, if a control arm (control group) had been included:
It would have revealed a higher incidence of mortality in the active arm (the group receiving Clofibrate) compared to the standard of care or the second arm (the group not receiving Clofibrate).This evidence would have prevented giving Clofibrate to a large number of subjects, thereby reducing unnecessary mortality.

Clinical trials

- **Individuals with particular disease are randomly allocated into experimental or control groups. randomization is used to ensure that both groups are comparable with respect to all other factors except for the one under investigation.**

- **The experimental group is given the agent being tested and the control group is given either an agent in current use or a placebo**

- **Ideally both patients and the observers should be 'blind' to the treatment being given. This in order to reduce bias.**

In clinical trials, subjects should be randomly allocated to experimental or control groups.

Example Scenario:

- Suppose you are a physician with two groups of patients with type 2 diabetes:
- **The first group** consists of cooperative patients who comply with treatment, have well-controlled glucose profiles, and are generally easy to manage.
- **The second group** includes patients who are less cooperative, have poor compliance with treatment, difficult-to-control glucose profiles, and high HbA1C levels, which took significant effort to manage.

- If you are aware of a **new treatment** for type 2 diabetes and, based on your own judgment:
- You allocate the cooperative group to the new treatment.
- You leave the less compliant group on the standard of care
- This approach introduces bias and violates the principles of a clinical trial. خطأ كبير يلي عملته

In clinical trials, each subject must have an equal chance of being assigned to treatment A (experimental) or treatment B (control), regardless of their clinical profile. الصح

I have 300 patients with type two diabetes, I want to have 150 in each group, then computer programs will do randomization, for example subject 1, 3, 5, 7, 10, 15 will be given treatment A and subject 2, 25, 30, 32 will be given treatment B.

Random allocation ensures fairness, eliminates bias, and enhances the validity of the study outcomes

شرحناه من قبل بتقدر تتخطى هذه الجزئية

- When discussing **placebo**, it refers to a dummy treatment such as starch or any inactive substance.

- Example 1:

A clinical trial for the treatment of sub-clinical hypothyroidism compared thyroxine with placebo.

- Example 2:

during COVID pandemic, in the early phases there was no treatment yet for covid-19 so we were comparing the expiremental treatment with placebo rather than Remdesivir
, but it's **unethical** actually, and it's **not scientific**, it's **illegal** to compare the active treatment or the new treatment with Placebo, there's existing treatment (remdesivir),

- Example 3:

I want to test different antibiotics for different infections I should compare it with the existing treatment.
New treatment for hypertension we know that we have current guidelines protocols for management of hypertension, different medications, patient should not be in placebo. So if there is any evidence of effectiveness of an intervention for any disease we should not give placebo for comparison.

Ideally both patients and the observers should be 'blind' to the treatment being given. This in order to reduce bias.

- Ideally patients and observer should be blind, this is very important actually, in the same example when I did the clinical trial we have cross-over clinical trial, some patients started Placebo for months and they had the placebo effect they were feeling much better, they were more physically active, they have better mental health and they asked us to stop the blinding and they didn't want to go to the second phase of thyroxine, they were actually blinded they thought they were given an active treatment, we broke the blinding there in
- placebo. so this placebo effect will have an impact on the Judgment, so the patient should not know whether they are taking the active treatment or the placebo, they should not know whether they are taken this active treatment or the existing treatment, the investigator

- who is conducting the assessment also should not know, if they know that this is the active or this is the placebo they might not have a valid way of assessment. So we need to blind the investigator and the patient. Actually recently we have also **Triple blind, which means that we blind the patient, the investigator and analysis conducter (biostatistician).**

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- patient. Actually recently we have also Triple blind, which means that we blind the patient, the investigator and analysis conducter (biostatistician).

Clinical trials

- **Are studies of the effect of a specific treatment on patients who already have a particular disease**

- **They are used to evaluate the efficacy of a preventive or therapeutic agent in the treatment or prevention of a disease**

Preventive trials	clinical trials
focus on **preventing** / stop the **occurrence** or **recurrence** of a condition. Examples include: Administering aspirin to prevent the recurrence of myocardial infarction (MI). Providing vaccines to healthy pediatric populations to prevent infections.	, the primary aim is to **cure** a disease or to **control** its progression . For example, you provide treatments for conditions like hypertension, diabetes, or cancer to manage or eliminate the disease.
• trials can be on **healthy subjects** **preventive trials will assess the impact of different preventive measures**.	• studies on the effect of specific treatment on a particular **patient with disease.** • **clinical trial assesses the effect of control disease or to cure the disease.**

Clinical trials

- **Assessment of each subject must involve bias free accurate measure of outcome**

  - In clinical trials, it's crucial that the assessment of each subject is done in a way that is free from bias and provides accurate measurements of outcomes. The trial should clearly define both primary and secondary outcomes. For example, if you are testing a new treatment for diabetes, the primary outcome might be the change in HbA1c levels between the group receiving the active treatment and the control group (who would be on standard care). Secondary outcomes could include additional measures like quality of life or mortality related to the disease.

- **Both groups are followed over a defined period of time when the outcome is then measured in both groups.** Check next slide

Both groups are followed over a defined period of time when the outcome is then measured in both groups.

We have two ways for design

parallel design	crossover Design,
we have two groups, each group receive the treatment for a period of time, first group will receive treatment A for three months, the second group will be received treatment B for 3 months, then we'll make a comparison at Baseline after 3 months.	in Chronic illnesses (for example hypertension or diabetes) if we stop the treatment patient will go back to point zero, the first group will start treatment A for four months then stop taking it for short period to clear their body from the treatment, then have another four months of treatment B, the second group will start treatment B four months then washout period then they will have treatment A in the second four month. **The crossover design typically takes longer due to the washout period between treatments.**
one treatment, large sample size, for short period.	multiple treatment, small sample size, multiple periods so collectively it is long.

What trials assess

- Drugs
- Surgery
- Type of management

(to be seen by general practitioner or family physician, early referral versus late referral)

- New services

(to compare management of hypertension at the family medicine or at the Cardiac Centre at hospital X).

Why Clinical Trials?

1. **Most definitive method to determine whether a <u>treatment is effective</u>.**

-Provide stronger evidence of the effect (outcome)
compared to observational designs, with maximum confidence and assurance

- Other designs have more potential biases
- One cannot determine in an uncontrolled setting whether an intervention has made a difference in the outcome.
- Correlation versus causation

We have findings from the observational studies but when we conduct clinical trial, we find that these observations are not accurate.

Example: trials of hormone replacement therapy in menopausal women found no protection for heart disease, contradicting findings of prior observational studies

Examples of False Positives

1. High cholesterol diet and rectal cancer
2. Smoking and breast cancer
3. Vasectomy and prostate cancer
4. Red meat and breast cancer
6. Drinking water frequently and bladder cancer
7. Not consuming olive oil and breast cancer

Replication of observational studies may not overcome confounding and bias

We need to do a clinical trial to compare the two arms and to make a final conclusion.

Why Performed ?

2. **Determine whether experimental treatments are safe and effective under "controlled environments" (as opposed to "natural settings" in observational designs), especially when the margin of expected benefit is doubtful/ narrow (10 - 30%)**

The "margins of expected benefit" are about weighing the good vs. bad effects of a treatment, and when the risks (like kidney failure) are too high, even a beneficial treatment might be avoided in practice.

We have a great treatment for control of blood pressure
if you have two arms we can compare the incidence of serious or moderate adverse reactions such as mortality, liver impairment and renal failure, it is very important that we compare the two arms together, otherwise we'll miss these serious complications.

I will not give my patients a new treatment for hypertension although it has great control blood pressure but one every 1,000 subjects will have renal failure. if you have 100,000 patients in Jordan with hypertension, we expect that every year will have 100 cases of renal failure due to this new medication so I'm not using it in my practice.

RCT Disadvantages

- **Large trials (may affect statistical power)**
- **Long term follow-up (possible losses)**
- **Compliance**
- **Expensive**
- **Public health perspective ?**
- **Possible ethical questions**
- **As above, may take a long time.**
- **Must be ethically and laboriously conducted.**
- **Requires treatment on basis (in part) of scientific rather than medical factors. Patients may make some sacrifice**

Clinical trials: choice of Design

Depends on:

- Research Questions
- Research Goals
- Researcher Beliefs and Values
- Researcher Skills
- Time and Funds

Our choice in Clinical trials depend on the research questions objectives, and available funding as well.

Clinical trial: Study design

It is also related to:

- **Status of existing knowledge**
- **Occurrence of disease**
- **Duration of latent period**
- **Nature and availability of information**
- **Available resources**

Why it is important to look at status existing knowledge in conducting clinical trial? Because I want to compare the new innovative medication with the standard of care/the current practice/the current evidence, I want to compare to placebo and when I can I use placebo one, when I can't.

There are four phases for clinical trials,
before we see any medication or **before** we start using any medication in practice or the phases of clinical trials, we have **preclinical phase** before.

So easy!! بصوت الدكتور سهيل زميلي

Preclinical

- **Biochemical and pharmacological research.**
- **Animal Studies**

Consists of animal studies that determine the toxicity and bioavailability of a drug. Studies involving animal matrices such as rabbit serum, monkey urine, dog or rat plasma, are all examples of preclinical studies.

example if we have new treatment for type two diabetes, we induce type two diabetes in the animals in the lab and see the effect of this treatment is it safe or not? what's the bioavailability of this medication? if the treatment passes this preclinical phase, we'll move to the phase one.

Phase I Trials

- **Clinical pharmacology- when the drug is given to healthy people estimate toxicity rates using few (~ 10 - 40) healthy subjects.**

The primary objectives of phase I clinical investigation are:

- **Determine the metabolism and pharmacologic activities of the drug in humans**
- **Side effects associated with increasing doses**
- **Early evidence on effectiveness**
- **Obtain sufficient information about the drug's pharmacokinetics and pharmacological effects to permit the design of well-controlled and scientifically valid phase II clinical studies.**

- we start **with one then two then three, we do not start with all subjects together.**
- For example, if I will test a new treatment for hypertension with those of 5 or 10 milligram. I'll give maybe 0.1 milligram to healthy subject to see the response, to see the pharmacokinetics, the safety in humans, execretion, metabolism, I'll assess all these things, on this **very small dose starting** with one subject then **I would increase the number of subjects**, I might increase the dose gradually but within **acceptable limits** because these are healthy subjects not those with the disease.
- **In phase one we know the safety for humans, we knew about metabolism, some side effects we can see based on this very small dose.**

Phase II Trials

- **Initial clinical assessment: determines whether a therapy has potential using a few very sick patients.**

The primary objectives of phase II studies are:

- **Identify accurately the patient population that can benefit from the drug.**
- **Evaluate the effectiveness of a drug based on clinical endpoints for a particular indication.**
- **Determine the dosing ranges and doses for phase III studies**
- **Common short-term side effects**
- **Risks associated with the drug.**

Phase III Trials

<u>Rigorous testing</u>: <u>large randomized controlled, possibly blinded, experiments</u>

The primary objectives of phase III studies are:

- **Gather an additional information about effectiveness and safety needed to evaluate the overall benefit-risk relationship of the drug.**
- **provide an adequate basis for physician labeling**

I will have large randomized control possibly double blind, triple blind clinical trial that I will have standard care versus this new treatment, there is no standard care treatment versus placebo, to see the impact of this treatment, I have two arms I assess the clinical outcomes, adverse reaction and this is what I need to ensure before I use this new medication in my clinical practice.

Phase IV Trials

- **Post-marketing surveillance: a controlled trial of an approved treatment with long-term follow-up of safety and efficacy.**

The primary objectives of phase IV studies are:

- **Provide additional details required to learn more about a**
- **drug's efficacy and/or safety profile.**
- **Study new age groups, races, and other type of patients.**
- **Detect and define of previously unknown or inadequately quantified adverse reactions and related risk factors.**

Improve treatment with long-term follow up of safety and efficacy. And to see the serious adverse reactions, then you can decide to keep it or remove it if it's proven that the new treatment is the cause of this adverse reaction.

So, I'm testing this medication for a particular group of patients for example patient with type two diabetes, with renal impairment or elderly subjects, The medication is already approved I'm using the medication in my practice I want to do extra long term follow up of safety and efficacy. I can study new groups, races, and other type of patients for this medication.

Types of Clinical Trials

- Randomized
  - Each subject in the clinical trial should have equal chance to be included in the study and we mentioned that there are software programs that will allow randomization
- Non-Randomized
  - should be avoided because we have here bias of selection in the study, and it will affect the outcomes of the study)
- Single-Center
  - (we are doing the study at one Hospital)
- Multi-Center
  - (can be two types: multi-centre **within the same country** and multicentre in different hospitals from **different countries)**
- Phase I, II, III, IV Trials **+ phase 0 (preclinical)**

Purpose of Control Group

- To allow discrimination of patient outcomes caused by test treatment from those caused by other factors
  - **Natural progression of disease**
  - **Observer/patient expectations**
  - **Other treatment**
- Fair comparisons
  - **Necessary to be informative**
  - **Comparison with currently approved treatments**

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Why Have a Control Group?
A control group is essential in clinical trials to ensure accurate evaluation of the effectiveness and safety of a new treatment. Here's an explanation using the **example** of tension headache:

- **Spontaneous Recovery:**

If you have 100 students with tension headaches and leave them untreated for 5-6 hours, around **30%** of them might **recover naturally without any intervention.**

- **Placebo Effect:**

If you provide a placebo (e.g., starch) and inform patients it's a treatment for headaches, an additional **10-20%** might improve due to the placebo effect.

- **Novel Treatment**:

A new treatment for tension headaches might resolve headaches in **80%** of patients within 10-20 minutes.

- **Importance of Comparison**

It's crucial to compare the **80% effectiveness** of the novel treatment to the **20-30% improvement seen in the placebo or untreated groups**, rather than comparing it to zero improvement contol يعني مع ولا حدا او بمعنى آخر ما عملنا Group . Comparing to zero would overestimate the treatment's effectiveness, as it ignores natural recovery and placebo effects بالتالي تقديراتنا غير دقيقة ارجع السطر الأول الكلمة يلي تحتها خط

- **Standard of Care: existing treatment بما معناه ال**

You also need to compare the new treatment with the current standard of care to understand its added value. This helps determine whether the new treatment is significantly better and justifies its potential use.

- **Cost vs. Benefit:**

If the new treatment is more expensive but only slightly more effective than standard care, you must evaluate whether its adoption is cost-effective.For example, if the differences in outcomes are small, the higher cost might not justify switching to the new treatment.

Adverse Reactions:
A control group is necessary to monitor and compare the adverse reactions between groups. This ensures a full understanding of the risks and benefits associated with the new treatment.

Natural Disease Progression:
Including a control group accounts for the natural progression of the disease, preventing bias and providing a clearer picture of the treatment's true impact.

باختصار

Conclusion:A control group allows researchers to:Accurately measure the treatment's effectiveness.Assess the cost-effectiveness and adverse reactions.Avoid overestimating the outcomes due to natural recovery or placebo effects.

Randomized allocation

- Like tossing a coin
- Avoids choosing
- Permits fair comparison

Randomized Controlled Clinical Trial

- Reference: Byar et al. (1976)

  New England Journal of Medicine

- Patients assigned at random to either treatment(s) or control

- Considered to be “Gold Standard”

In randomized allocation each subject will have the same chance to be included in this study كم مرة صرنا حاكيين هاي النقطة!!!!!!

Ethics of Randomization

- Statistician/clinical trialist must sell benefits of randomization

- Ethics ⇒ MD should do what he thinks is best for his patient
  - **Two MD's might ethically treat same patient quite differently**

- Chalmers & Shaw (1970) *Annals New York Academy of Science*

1. **If MD "knows" best treatment, should not participate in trial**
2. **If in doubt, randomization gives each patient equal chance to receive one of therapies (i.e. best)**
3. **More ethical way of practicing medicine**

- **Bayesian Adaptive designs → More likely assign "better" treatment**

Ethics of randomization; we should ensure equal chance otherwise it is unethical to do the trial.
باختصار كما يقول المثل الشهير مش خيار و فقوس مش عارف اذا المثل اله دخل او لا

Ethical imperatives

- Must be real doubt
- Obtain inform consent
- Preserve clinical freedom

حديث عبد الله بن مسعود قال :قال رسول الله :ﷺألا أخبركم بمن يحرم على النار، أو بمن تحرم عليه النار؟، تحرم على كل قريب هين لين سهل

I should not test any treatment in humans if I don't have a real doubt that this new treatment will be worthwhile, البشر مش لعبة تعمل عليهم تجارب حتى تتسلى فقط إذا كان فعلا في معضلة و بحاجة إلى إجراء هذا النوع من التجارب

we should have informed consent, patient should agree that they are willing to take part in the study. لازم تاخد موافقتهم

I should preserve clinical freedom, I should inform them (even it is written down the consent form) that if you decline take part in the study or if you withdraw of the study this will not affect your participation in the clinical trial.

- يعني لا تشخصن مع المتطوع اذا قرر ينسحب او رفض إجراء معين مطلوب منه خليك مرن المتطوع اله الحرية انه يرفض و هذا لا يؤثر على تقديمك الرعاية الصحية اله او حتى انك تضايق عليه بالتجربة اذا قرر يكمل

لازم نتحمل بعض ياجماعة نحنا **بشر** بالآخر

Defining the patients

- Diagnostic features
- Eligibility criteria (inclusion and exclusion)

we should be clear about who should be included in my clinical trial,
Examples diagnostic features

- someone with Hb1Ac equals 10 to 14 ,
- TSH 4.5 until 10,
- systolic blood pressure above 180 or diastolic above 100.

We should have clear diagnostic features and eligibility criteria.

- In clinical trials, **diagnostic features** identify patients with the **target condition**, while **eligibility** criteria help define who can safely and effectively participate in the study, even if they meet the diagnostic features.

Assessing the outcome

- Clinically relevant
- Easily measured
- Accurately measured

Cure rate, mortality rate, quality of life all should be accurately measured and easily measured and clinically important.

Types of outcomes

- Death
- Clinical measurement
- Symptoms
- Quality of life
- Psychological wellbeing

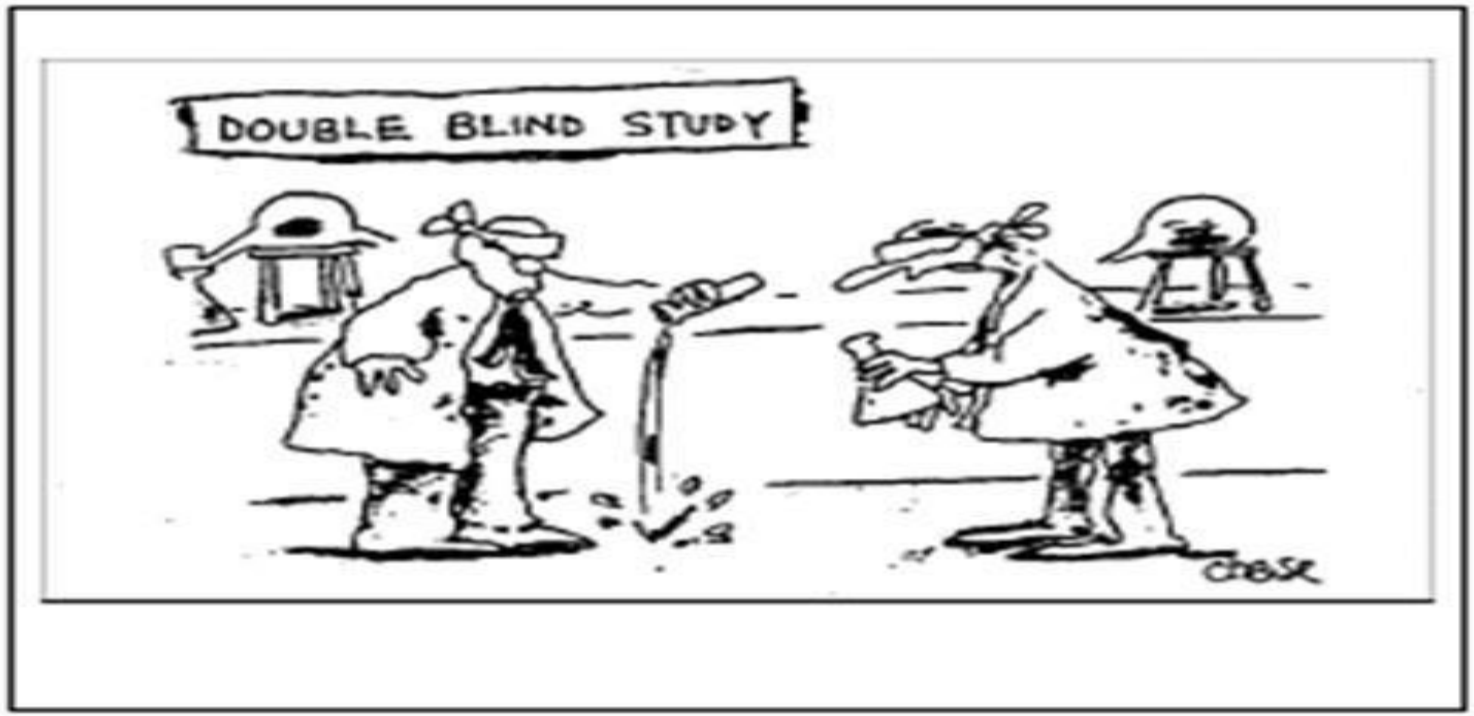
Types of outcomes can be death, can be clinical measurement, Pain Scale, any clinical parameters, symptoms, quality of life, psychological wellbeing.
The most important thing is that these things should be valid tools for assessment

The need for blinding

- Open

(no blinding)

- Single blind
- (I can blind the patient on the investigator or investigator the patient) برضو انا ما افهمت
- Only one party is blinded, and most commonly, it is the participant (patient) chat gpt
- Double blind
- (patient and investigator will be blinded)
- Triple blind
- blind the investigator + the patient + also the person doing the analysis who has the data for treatment A and treatment B, he also should not know which is which)


DOUBLE BLIND STUDY

Definitions

يلي حكينا عنهم قبل شوي

- **Single Blind Study**: A clinical trial where the participant does not know the identity of the treatment received
- **Double Blind Study**: A clinical trial in which neither the patient nor the treating investigators know the identity of the treatment being administered.
- **Triple Blind study: Biostatisticians is also blinded**

Definitions

- **<u>Placebo:</u>**
  - Used as a control treatment

    1.An inert substance made up to physically resemble a treatment being investigated

    2. Best standard of care if "placebo" unethical(We only use Placebo when there is no standard of care)

    3. "Sham control": Faked surgical intervention with the patient's perception of having had a regular operation

    means to make the patient feel that he had any sort of surgical intervention compared with medical treatment and he had fake surgical intervention to ensure the blinding).

Definitions

- **<u>Adverse event:</u>**
  - An incident in which harm resulted to a person receiving health care.
  - **Examples:** Death, irreversible damage to liver, nausea
  - Not always easy to specify in advance because many variables will be measured
  - May be *<u>known</u>* adverse effects from earlier trials

If we have in Phase zero, one or phase two serious Adverse events, we should not proceed to phase three.

Surrogate Endpoints

- **Response variables used to address questions often called <u>endpoints</u>**
- **Surrogates used as alternative to desired or ideal clinical response to save time and/or resources**
- **Examples**
  - Suppression of arrhythmia (sudden death)
  - T4 cell counts (AIDS or ARC)
  - Cholesterol (heart disease)
- Often used in therapeutic exploratory trials
- Use with caution in confirmatory trials

- **Surrogate endpoints** are indirect measures used in clinical trials to predict the long-term effects of a treatment without waiting for the actual outcomes.

- **For example**:

In a study on a new treatment for hyperlipidemia: The treatment reduces lipid levels by 10%. Instead of waiting 10-15 years to observe its impact on ischemic heart disease, researchers use the lipid reduction as a surrogate endpoint to estimate its potential effect on heart disease incidence.

This method allows quicker evaluations while still providing valuable predictions.

Summary of trial design

- Specify the treatment
- Define study group
- Random allocation
- Blinded outcome assessment
- Fair interpretation

Clinical trial

Common problems

- Too few patients
- Failed randomization
- Patients lost to follow-up
- Flawed analysis-interpretationr

efers to incorrect or misleading conclusions drawn from the data or results of a study

(that's why actually now we have phase three clinical trial)

- Power of study: not big enough

(and the study may be not big enough to find this significant difference

Cross-over clinical trial

شرحناه قبل شريحة رقم ١٩

Each patient gets **both treatments**

Half get A then B

Half get B then A

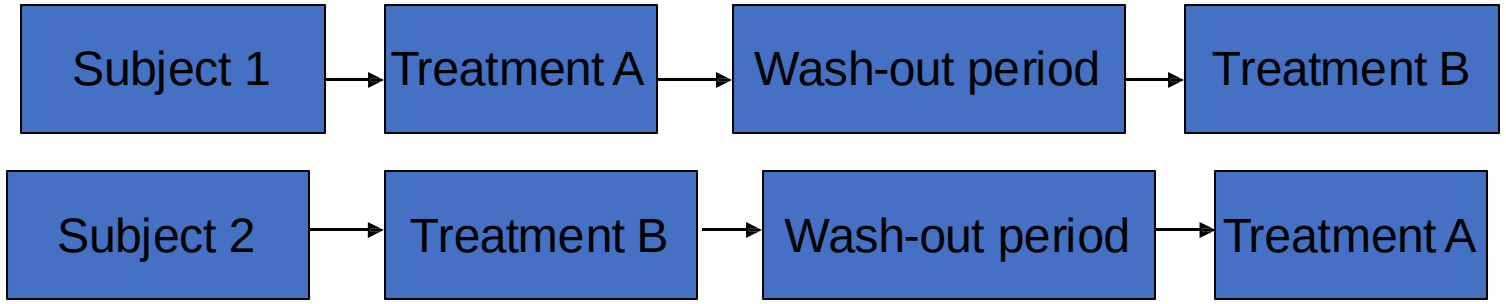
Wash-out period in between

In diseases like hypertension, diabetes, or arthritis, when treatment is stopped, patients often return to their baseline condition. To account for individual variation, the ideal approach is to use a crossover design, where each patient receives both treatments (A and B) in sequence, compared to their own baseline. This reduces the sample size needed but requires a longer study duration.

Crossover Design: Patients receive Treatment A, followed by a washout period (usually 4 half-lives), then Treatment B

Parallel Design: Patients receive either Treatment A or Treatment B (but not both).

The crossover design typically takes longer due to the washout period between treatments.



Cross-over clinical trial

- Cross-over design
- Patient as own control

-Reduce variations

-Much smaller sample size

Requirements: Carry over period(s)

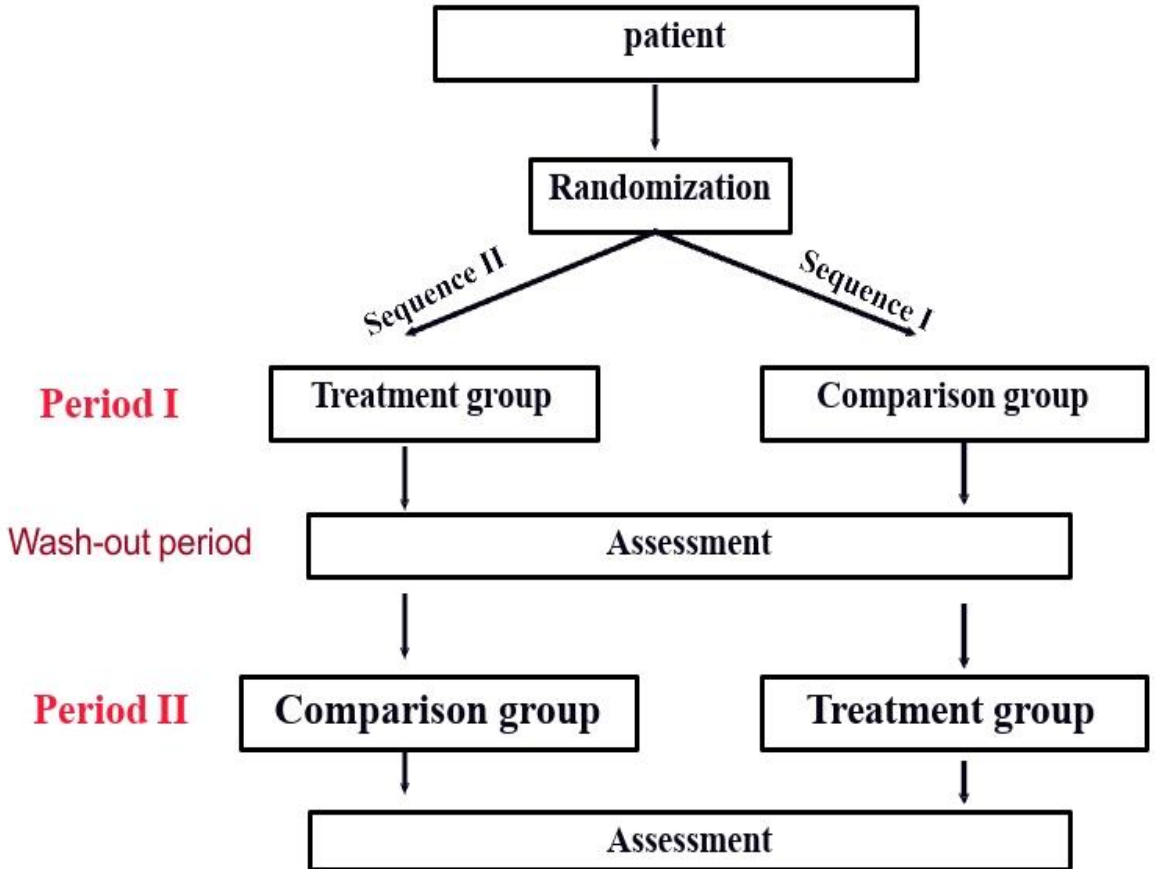
Key elements of RCTs

- Selection of subjects
- Comparison group
- Randomization
- Allocation of treatment
- Blinding (single, Double blind design/placebo)
- Intention to treat analysis in which the treatment and control groups are analyzed with respect to their random allocation, regardless of what happened subsequently

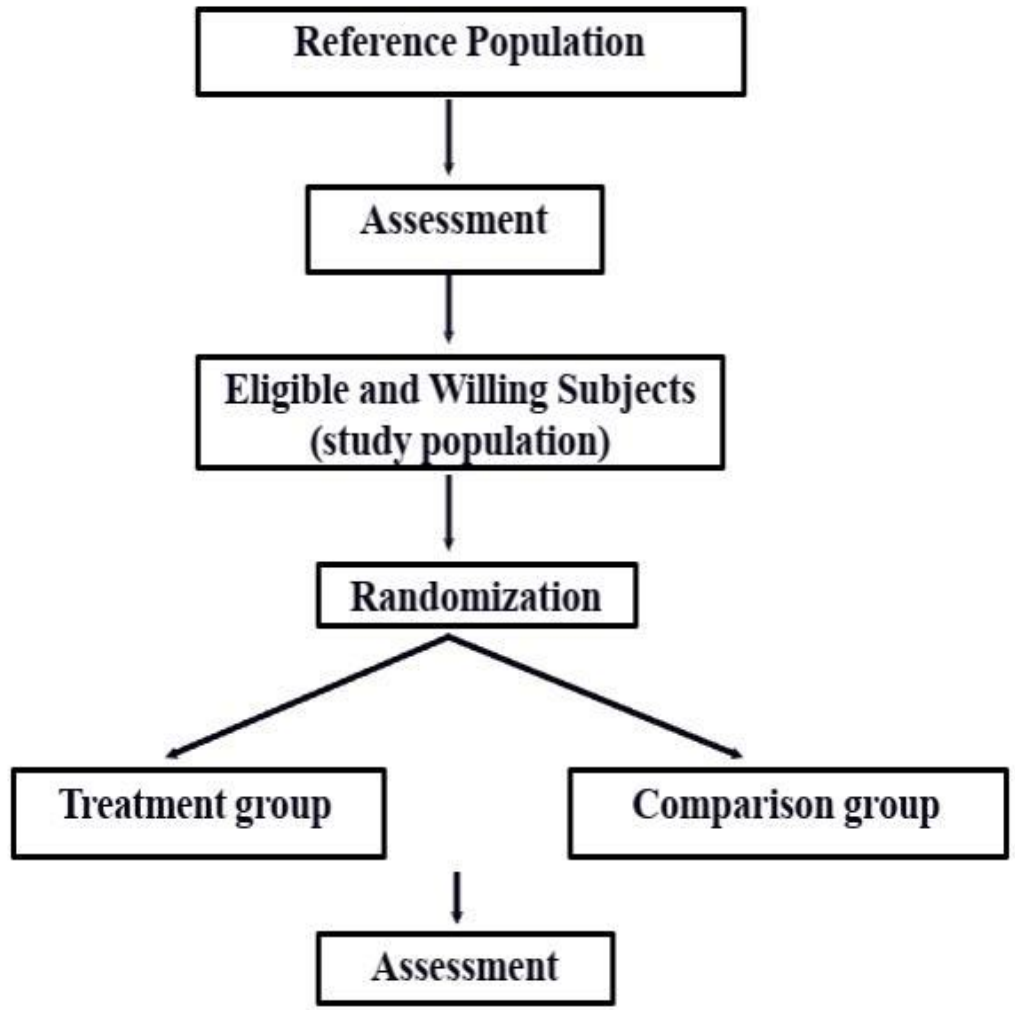
- Ethical considerations

In a study where you start with 200 subjects but end with only 120, it's important to investigate what happened to the **80 subjects who were lost. These participants should not be excluded from the** analysis, as their data could provide valuable insights into the study's outcomes. For example, they might have left the study due to serious adverse reactions or other reasons. Understanding the reasons behind their withdrawal is essential for accurate interpretation of the study results, ensuring that the analysis reflects the true impact of the treatment.

Crossover Design



Parallel Design



Preventive trials

Are studies of the effect of a possible preventive measure on people who do not yet have a particular disease.

Another type of preventive trial is a study of the effect of a possible preventive measure on whole community

Preventive trials

- **The risk of developing any particular disease among the people who are free from disease is small. Because of this, preventive trials usually require a greater number of subjects than clinical trials, and are therefore more expensive**

for example new vaccine for prevention of influenza, we might need 50,000 subjects to participate in the trial to look at the incidence of influenza, so this is more expensive, and we need more resources.

- **This expense limits their use to the study of preventatives of extremely common or extremely severe diseases**

  e.g. vaccination to prevent whooping cough

  vaccination to prevent poliomyelitis

- **When a disease occurs rarely, it is more efficient to study those people thought to be at high risk of disease , e.g. vaccine to prevent Hepatitis B**

because incidence of the disease will be higher in them, So we don't need to have much larger sample size.

Preventive trials

- **As in clinical trials, the preventatives should be given so that the individuals who do and do not receive the preventative are as comparable as possible. This is often difficult.**

- **In some types of trials the preventative have to be administered to communities rather than individuals, e.g. water fluoridation to prevent dental caries**

- if we give the intervention water fluoridation to prevent Dental carries this is what we call the Community trials, let discuss it in a minute.
- ➢ **Preventive trials is an introduction to community trials**

Results of a trial to determine whether A vaccine could prevent whopping cough

- we can look at the incidence among these two groups, we can see that incidence is much higher among nonvaccinated.

	No. with Whooping cough	No. without Whooping cough
Number vaccinated 3801	149(4%)	3652(96%)
Number not vaccinated 3757	687(18%)	3070(82%)

Community Trials

- **A community participates in a behavioral intervention, nutritional intervention, a screening intervention, etc**
- **Intervention: Any program or other planned effort designed to produce changes in a target population.**
- ***Community* refers to a defined unit, e.g., a county, state, or school district.**
- **Communities are randomized and followed over time.**
- **Determine the potential benefit of new policies and programs.**

Examples:

- **A community-level intervention for tobacco control might combine a school curriculum for youth to prevent initiation of smoking**
- **A media campaign aimed at reducing smoking rate**

Examples

- Smoking cessation interventions for secondary schools
- Medical Research participation interventions: one for JU and another intervention for JUST

- Increasing fluoride level within acceptable limits in all drinking water sournces in Aqaba and comparing with Irbid, keeping this as they are.

Primary outcome: dental cases incidence for children younger than the age of 5.

- **In clinical trials** we talked about randomizing patient with type two diabetes, patient with hypertension and we have 300 subjects, and you **randomize them one by one**.

- **Community trials** we are talking about the whole Community. Same to the examples of online lectures in Mafraq and Irbid that I mentioned at the beginning.

- So here we have intervention for the whole Community not for individual subjects and we **randomize based** on the **community** not based on the subjects and this is the end of our lecture, thank you very much.

Links for meta-analysis and systematic reviews: from the doctor

https://youtu.be/egJlW4vkb1Y?si=TBei4Ts6D6I5c9hp
https://youtu.be/pYDAN8MRY-w?si=bTLcnJmmyztRPOCG
https://youtu.be/TLvF80WIXX8?si=Jpj1UgkCalHmxL9n

حديث عبد الله بن مسعود رضي الله عنه قال :قال رسول الله ﷺ: ألا أخبركم بمن يحرم على النار، أو بمن تحرم عليه النار؟، تحرم على كل قريب هين لين سهل

Additional sources

فيديو لتغيير الجو بعد هذا الملف الطويل

https://youtu.be/VORGG69mWD0?si=PUj34i5-jH9UCBt0

VERSIONS	SLIDE #	BEFORE CORRECTION	AFTER CORRECTION
V1→ V2			
V2→V3			

امسح الرمز و شاركنا بأفكارك لتحسين أدائنا !!