MEDICAL RESEARCH

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Week 7

Hello everyone, this week we will cover mainly the experimental studies.

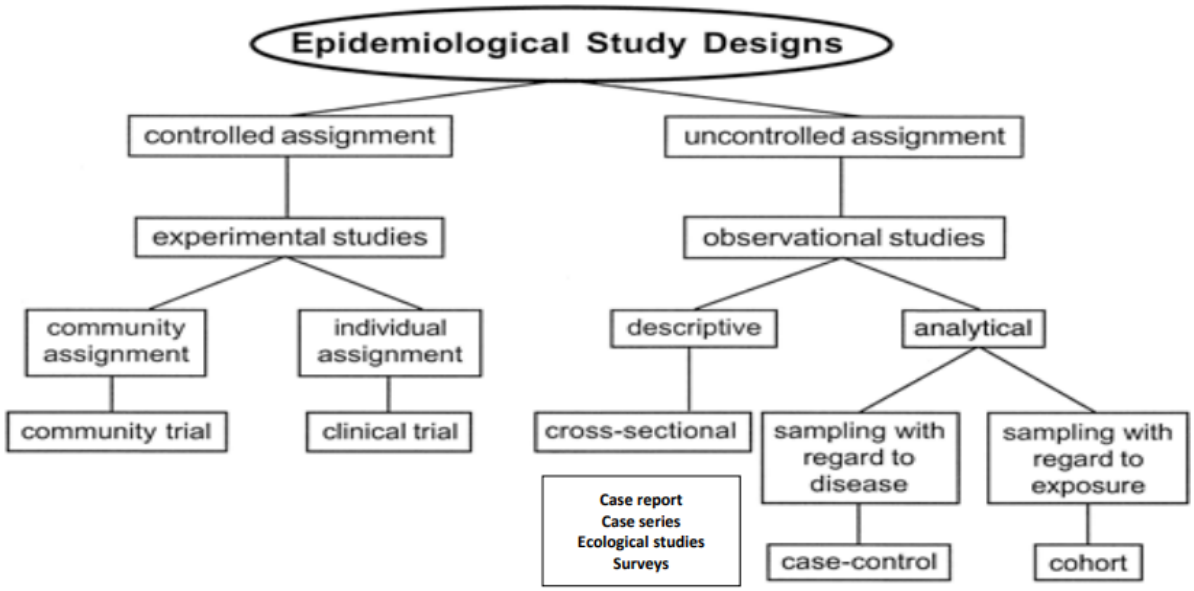
When we have different cross-section studies looking at for example the prevalence of Hypothyroidism in different countries and we want to have just one figure related to the global prevalence of hypthyroidism, we can combine these different studies together in what we call meta-analysis technique to come up with an overall prevalence of 5% / 10% / 3% worldwide. again, we are combining data from different individual studies to produce one summary estimates the overall effect, this is what we call Meta-analysis.

So, in meta-analysis we combine the results, but in systematic reviews we can't combine them. Chat GPT says that in both methods, systematic review and meta-analysis, we can combine the result. But the doctor mention them as above.

We have different clinical trials conducted on treatment X for the treatment of type two diabetes, and you have seen different clinical trials conducted over the last three years and we want to combine these clinical trials in one finding, and there is no heterogeneity between these studies and you want to combine them together you'll have one outcome that will show the result, this is what we call meta-analysis. if there is heterogeneity between these studies and we can't combine them together and we show the results in one table or two tables, this is systematic reviews.

The highest evidence in medical research or in evidence-based medicine is coming from meta-analysis and systematic reviews, followed by clinical trials. (we combine different clinical trials together to be one unit stronger than a single clinical trial that's the meta-analysis).

Going back to this figure that I will keep always showing this figure because this is the key thing that you need to know to differentiate between different studies.



We classify studies into controlled assignment and uncontrolled assignment. **Controlled assignment**: as an investigator, you will have an impact, you'll control something, you'll change something, you'll do something. **Uncontrolled assignment**: it is just an observational study, we don't have any intervention.

We can give group A treatment X, and Group B the standard treatment or Placebo (Placebo is an inactive substance or treatment that lacks any therapeutic effect like sugar pills and saline injections)

The experimental studies are not just given treatment. for example, if you want to have a clinical trial or experimental study to see the impact of early referral physiotherapy for patient with severe low back pain you'll have two groups : group A will have severe low back pain and we give them this early physiotherapy and they'll be seen within 48 Hours (let's refer to this group as Arm A) , and Arm B (another group) will be treated with the standard referral physiotherapy. and you'll assess the impact of this early referral

versus standard referral after six weeks to see the impact in quality of life or Pain Scale.

جراحة بالمنظار

I want to compare open surgery versus laparoscopic surgery. Another example.

so I want to see if you have newly diagnosed diabetic patients and want to compare general practitioners with family physicians to see the impact of management 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.

Also, we can compare patients on same medication on different doses, we can compare different treatments, this is the controlled assignment, as an investigator I will have role there, a referral versus late referral, treatment A versus treatment B Etc…

In experimental studies also we have two types as shown in the figure, **Community assignment** and **individual assignment.**

Individual assignment: we have clinical trial, preventive trial, I'll give the patient this treatment and the other patient the standard treatment or placebo.هون بنقارن بين شخص و شخص

Community assignment: we are talking about group of patients, for example, I want to see the impact of two interventions for improving medical students research participation, at Jordan University جامعتنا الأم, I'm going to give medical students some online lectures at the start of the first term, and I will see the number of studies they conduct at the end of the year.

At Jordan science technology يعني جامعة التكنو I'll will not give them online lectures, I'll give them just some leaflets or posters about the importance of research and encouraging students to take part in

research. I want to compare these interventions together. this is a community trial. احنا هون بنقارن بين مجموعة طلاب ومجموعة طلاب ثانية

I want to see interventions for smoking cessation among teenagers, I'll see students in Mafraq يعني مدينة المفرق I will give lectures to students at secondary schools in Mafraq give them different lectures and seminars about smoking and we'll assist the smoking prevalence at the start of the program and at the end of these intervention at one year time. in Irbid يعني مدينة اربد the intervention there will be just posters, leaflets to students. So I'll compare these leaflets and posters that will be handled to Irbid's Secondary Schools students compared with the lectures that will be given Mafraq. here I'm not talking about individual persons.

A classical example, if I want to increase fluoride level in the water supplies in Aqaba يعني مدينة العقبةwithin the acceptable معلومة طبية : زيادة الفلور بقلل تسوس بالاسنان I assess the incidence of dental carries for children younger than the age of five over the coming three to five years, after five years for example, I compare it with incidence of dental carries for example in in Karak و هي جبنا سيرة الكرك عشان الكركية ما يزعلوا I'll keep the fluoride level within the normal status (without any increase).

The previous intervention was to increase the fluoride within an acceptable limit in all water supply an Aqaba, so here we are not talking about individual patients, I'm talking about the whole population, this is the community assignment.

This was a brief description of experimental studies. okay we'll start with the slides;

Experimental Study Design: is 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).

When we have a clinical trial for example, there is an existing treatment (for example for hypertension) and I have new better intervention to control of blood pressure, I should not compare the new intervention with placebo, I need to compare it with the existing treatment, but if you are treating a disease with no cure (no existing treatment) here you can compare the intervention with placebo.

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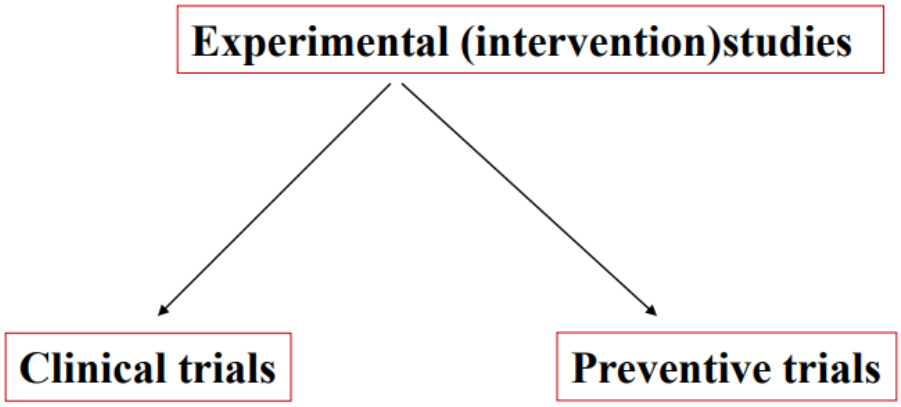
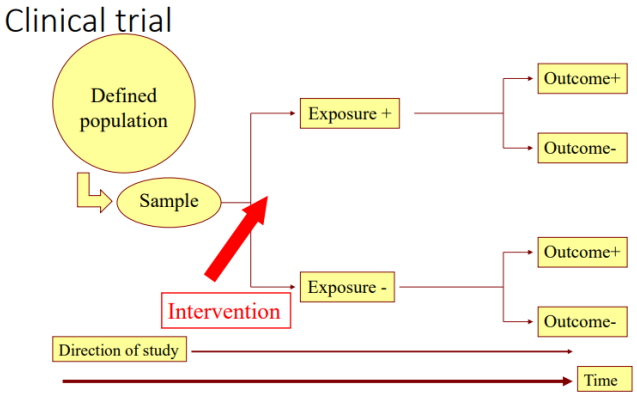


Here, the clinical trial & preventive trials, in **clinical trials** you give treatment to cure the disease or to control the disease, while the **preventive trials** are experimental studies to prevent something, for example we give aspirin to prevent recurrence of MI (myocardial infarction) or we'll give a vaccine to prevent infections among healthy pediatric age groups for example, **So** preventive trials will prevent something, in clinical trials we control or cure a disease.

Experimental Study Design is 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 observation designs we need to do something, we'll have exposure, we'll give aspirin, we'll give treatment, and we'll do random allocation of the subjects which means that each subject in the study should have equal chance to be in treatment A or treatment B.

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 ex; Clofibrate: Successfully lowers cholesterol Treated group: reduced CHD incidence, but higher all causes mortality.**
- **Spontaneous improvements**
- **Importance of small effects**

Experimental study are needed actually to show the impact of different interventions, if we have no control group and no clinical trial we might have serious adverse reactions that we are not observing, for example the Clofibrate which successfully lowers cholesterol levels and we give it to one arm (one group of subjects) and they had some mortality there and they thought this is unknown cause of mortality or they have mortality due to other reasons not due to Clofibrate. but if they had a control arm (control group) they'll find that there is a high incidence of mortality in the active arm (the group who took clofibrate) compared with the standard of care or the second arm (who does not took clofibrate), so we would not have

given the Clofibrate to high number of subjects in order to prevent mortality.

▪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.

In clinical trials, subjects should be randomly allocated to experimental or control groups. If I'm physician and I have for example two groups of patients with type two diabetes, the first group are cooperative subjects, they complying with treatment, well controlled and everything is perfect there, on the second group they have patient difficult and poorly complying with indication, their glucose profiles difficult control and we have Hb1AC is high and it took me a while to control their Hb1Ac. if I know there's a new treatment for type two diabetes and I know the groups and I can control them and can allocate them based on my own judgment I will give the Cooperative group the new treatment and keep the less compliant subjects or difficult control subjects on the standard of care, because it took me a while actually to control their profile clinical trials I should not do that. Each subject in the trial should have equal chance to be on treatment A or B.

يعني لازم يكونوا العينات عشوائية وما تحط مثلا المرضى الي بتحسنوا عالسريع بمجموعة لحالهم وتجرب عليهم العلاج الجديد , والمرضى الي ما بتحسنوا تحطهم كلهم مع بعض وتعطيهم العلاج المعتاد, عشان بس تحكي انه العلاج الجديد تبعك اشتغل.

For example, 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.

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

وهمي

When we talk about placebo, placebo is dummy thing like for example starch, I did clinical trial for treatment of sub-clinical hypothyroidism, we're comparing thyroxine with Placebo. Just an example.

Another example, 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 (اسم دواء بعالج اعراض الكورونا) for example, 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), for example 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).

We have the patient is blinded, the investigator is blinded, the biostatistician is blinded, but there must be someone else in the study team who knows the patient number and the treatment is taken currently (the active treatment or Placebo), so someone within the research team should know who's on the active treatment and who's in the placebo or the second treatment.

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.

Clinical trials are studies on the effect of specific treatment on a particular **patient** with disease. But **preventive** trials can be on **healthy** subjects like vaccines on children to prevent for example pneumonia infections or influenza infections and they are healthy, they don't have a disease. Also you can have preventive trial on subjects for example MI to prevent recurrent MI. so preventive trials will assess the impact of different preventive measures. clinical trial assesses the effect of control disease or to cure the disease.

▪Assessment of each subject must involve bias free accurate measure of outcome.

Clinical trials should have primary, secondary outcomes, I have for example new treatment for diabetes, I want to assess the Hb1Ac between the active treatment and the control group who are on the standard of care treatment, I want to assess quality of life, mortality

for disease, I should be bias free accurate measurement of the outcome.

▪ **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 actually, we have the parallel design and crossover design, in **parallel 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, we conduct something we call **crossover Design**, 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.

Parallel design >>> one treatment, large sample size, for short period.

Cross-over design >>> 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 we conduct Clinical Trials?

1. **Most definitive method to determine whether a treatment is effective.**

-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.

Other examples of False Positives of observational studies:
1.High cholesterol diet and rectal cancer
2.Smoking and breast cancer
3.Vasectomy and prostate cancer
4. Red meat and breast cancer
5.Drinking water frequently and bladder cancer
6.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.

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%)**

We have a great treatment for control of blood glucose, control of rheumatoid arthritis, of diabetes, of ischemic heart disease, 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 (randomized clinical trials) 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.

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.**

we have four phases for clinical trials, before we see any medication or before we start using any medication in practice, we need to see the phases of clinical trials, but before we have **preclinical phase:** we have a new potential molecule or treatment so initially we test it on animals to see whether it will work in animals? what's this toxicity? Bioavailability?…for 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.

Phase one is clinical trial in known healthy subjects 10-40 Healthy subjects for example, 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.

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.

In phase one we knew the safety for humans, we knew about metabolism, some side effects we can see based on this very small dose. Now I want to see when to start with the initial clinical assessment, is this treatment has a potential for using in very few sick patients? Can be used for poorly controlled diabetic patient, ill cancer patient. So I must identify accurately the patient population who can benefit from this treatment, evaluate effectiveness of the drug based on clinical End point, particular indication, I can test different doses actually that I'll use in phase three clinical trial, I look at common short-term side effects and risks.

Phase III Trials

Rigorous testing: large randomized controlled, possibly blinded, experiments.

- **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 labelling.

This treatment is working fine, I can see that those of 5 - 10 mg is working for my patients, 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.

We have start using the medication, I need to do Post marketing surveillance and 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** (we need to ensure that we have randomized clinical trials, 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** (we need to avoid non-randomized, 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** also we have phase zero on animals (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**

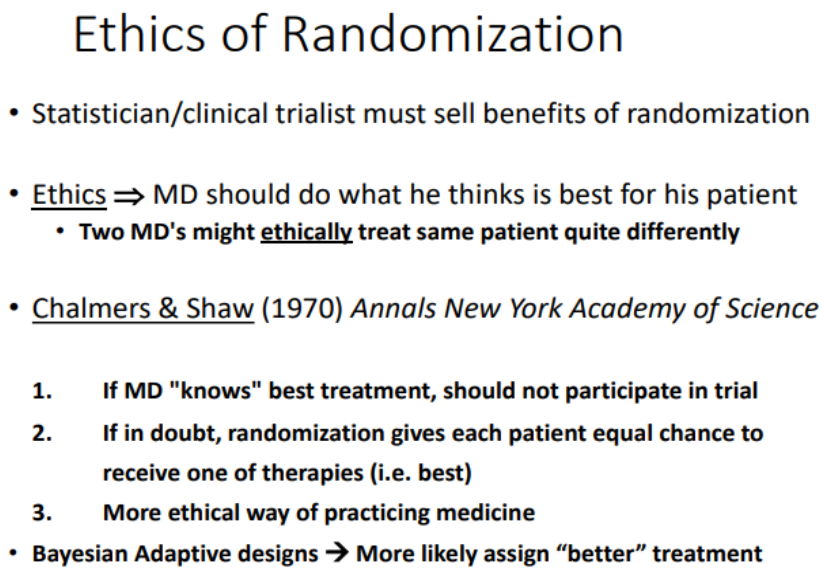
Why you have a control group actually? I'll give you a simple example and if we have 100 students with tension headache, if you leave them five-six hours maybe 30% of them their headache will resolve spontaneously, if you give them placebo like starch and you tell them this is a treatment for headache maybe they will quickly improve for 10-20% of them. if you have an novel treatment for tension headache and give to them you see will see the impact is 80% of them could resolve within 10 minutes or 20 minutes for example, I want to compare this 80% with 20% or 30% that will resolve, not with zero because I will overestimate the outcome this treatment if I compare it with nothing, so I need to compare this new treatment with the standard of care to see the differences, maybe the new treatment is much more expensive and there are small differences in the outcomes of my study, so I need to ask myself whether it's worthwhile to have this new treatment or not based on the cost only and also we need to look at adverse reaction incidence between the groups, so it's very important to compare the outcomes and also to look at adverse reactions and also to avoid the natural progressional of the disease.

Randomized allocation

• Like tossing a coin

- **Avoids choosing**
- **Permits fair comparison**
- **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.



Ethics of randomization; we should ensure equal chance otherwise it is unethical to do the trial.

Ethical imperatives

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

I should not test any treatment in humans if I don't have a real doubt that this new treatment will be worthwhile, we should have informed consent, patient should agree that they are willing to take part in the study. 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.

Defining the patients

- **Diagnostic features**
- **Eligibility criteria (inclusion and exclusion)**

we should be clear about who should be included in my clinical trial, someone with Hb1Ac equals 10 to 14 for example, TSH 4.5 until 10, systolic blood pressure above 180 or diastolic above 100. We should have clear diagnostic features and eligibility criteria.

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)
- **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)

Definitions

- **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**

Placebo:

- **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).

Adverse event: **is 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 known 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 endpoints**
- **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**

It is very important to understand what Surrogate Endpoints are, for example we have a new treatment for hyperlipidemia, it reduces lipid profile by 10%, it will take us actually very long time maybe 10-15 years to see the impact of this treatment on incidence of ischemic heart disease, so we make what we call Surrogate Endpoints which is an estimation based on this change in lipid profile to look at the expected change incidence of ischemic heart disease.

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-interpretation** (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)

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In many diseases like hypertension, diabetes, arthritis. if you give treatment then you stop, the patient will go back to the Baseline. so the ideal way is to compare each patient with himself or herself to

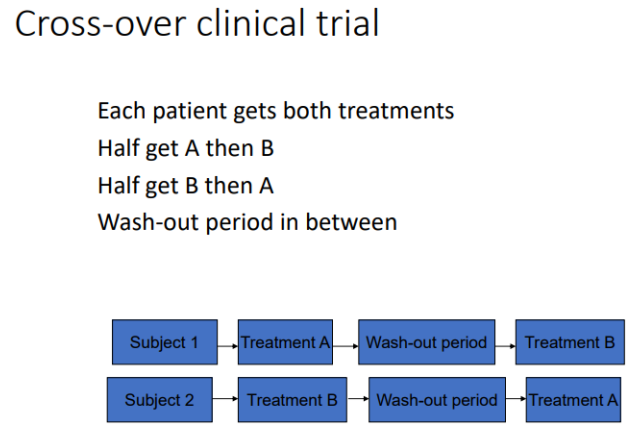
avoid variation between the patients, and we'll have smaller sample size but we need a longer duration because we'll have first group receiving treatment A then washout period depending on the half-life of the treatment A, we'll have four half lives to get rid of this treatment then you start treatment B.

if we missed the washout period the patient will have combination treatment because the treatment is still in their body that's why we need to have a period here to get rid of the previous treatment).

The second group will be **randomly allocated**, start with treatment B, wash-out period then treatment A.

In this cross-over design the duration of the study will be longer than the parallel design.

In parallel design treatment A or B (not both), in crossover design treatment A then wash-out period then treatment B.

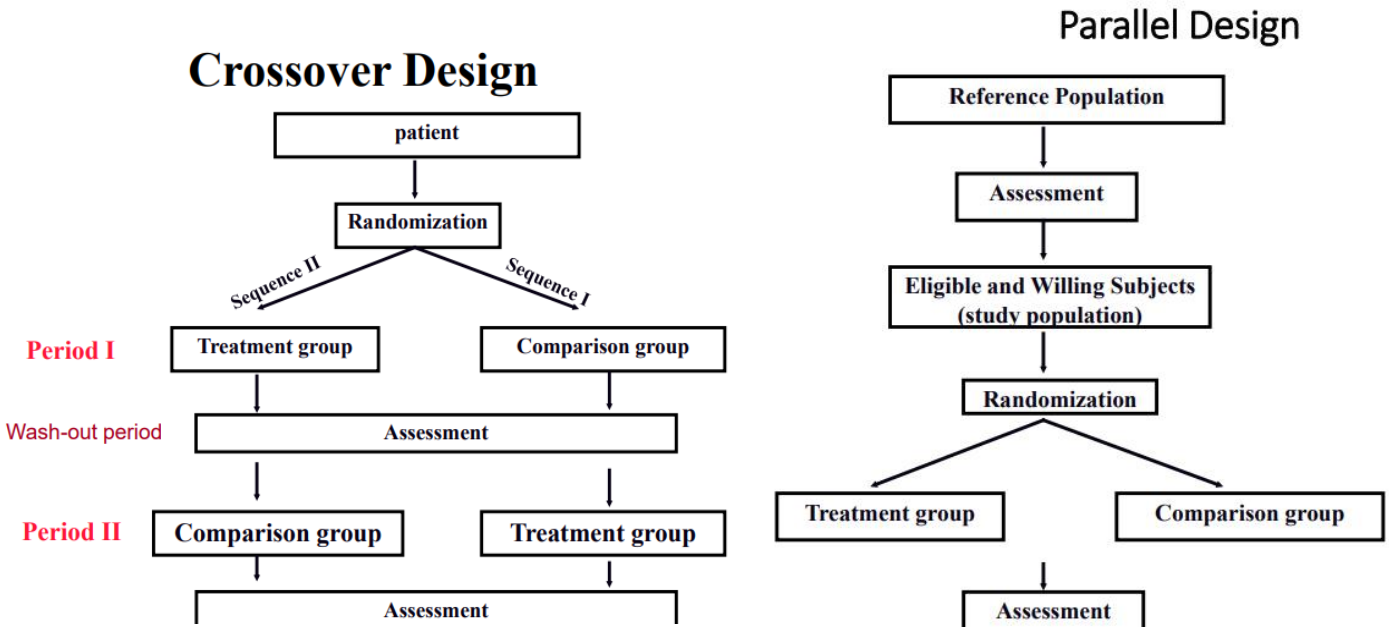


Cross-over clinical trial

- **Cross-over design**
- **Patient as own control**
- **Reduce variations**
- **Much smaller sample size and stronger study**
- **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** (You start with 200 subjects, but you ended by 120 subjects, what about these 80 subjects? they were lost in the study, we need to get information about them, maybe they left the study because of serious adverse reactions, we need to know what happened to them and to make assessment based on the data, we should not exclude them from the analysis).
- **Ethical considerations**



Moving from clinical trials to preventive trials where we prevent recurrent illnesses, we prevent disease among Healthy subjects.

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.

▪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.

If you want to study 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, because incidence of the disease will be higher in them, So we don't need to have much larger sample size. **e.g. vaccine to prevent Hepatitis B.**

▪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

This is the result of clinical trial on in cough. >>>>>

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

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

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

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.

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.
• 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.

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.

Best Wishes