بسم الله الرحمن الرحيم

هنالك نوعين من الدراسات الوبائية:

= uncontrolled assignment

1- Observational (no human intervention) دراسة مقطعية

a. Descriptive: Case Report, Case series, Cross-sectional, Ecological (correlational) ارتباطية

= measures of frequency

b. Analytical: Cohort, case-control

=measures of association → لقياس وجود رابط فعلي

دراسة رابط مع رابط آخر

هل يوجد علاقة؟ ← يمكن أن تكون حقيقية أو لا

2- Experimental (human intervention) → = controlled assignment

- Clinical trials → تجارب سريرية
- Community trials → تجارب مجتمعية

OBSERVATIONAL STUDIES

1. Descriptive studies are usually for obtaining information about the occurrence and pattern of a disease in a population & to generate hypothesis → لوضع فرضيات
2. Analytical studies: test cause–effect relationships (hypothesis) → تختبر الفرضية

الدراسات التحليلية — العامل المسبب — العلاقة بين

Clinical observation → Descriptive study → Analytical study → Experimental study

Both need data collection جمع بيانات

2 types of data collection:

A- Primary: collected by the investigator → less error and fits the study better but it will cost more أولية — الباحث

B- Secondary: collected by OTHERS → from individual (medical) or group records (census) سجلات طبية — سجلات مدنية — تعدادات سكانية

دراسة رجعية ← مستقبلية / استطلاعية

Prospective VS. Retrospective studies

Prospective: looking for the outcome (like development of a disease) in a specific period for a particular study group with suspected risk or protection factor

Advantages: more accurate دقيقة and reliable موثوقة because of direct access to study subjects

Disadvantages: long period of time and more cost, loss of subjects

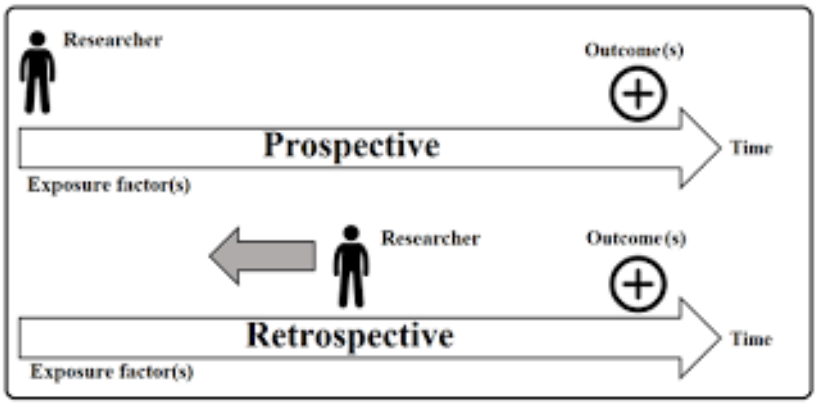
AKA = also known as
المقصود فيها بأكثر من مسمى آخر للمصطلح

Retrospective: looks backwards and examines exposures to suspected risk or protection factors

Advantages: Fast and cheap

Disadvantages: Recall bias (because it looks at the past, subjects may not remember)

Bias: تحيّز



Observational studies:

1. Descriptive

A- **Case report**: report about one patient

Example: a woman used oral contraceptive pills develops a pulmonary embolism

Can challenge after observation and then rechallenge (e.g.: suspecting drug might be producing specific symptoms, stop the drug then restart drug)

B- **Case series**: describes characteristic in several patients with a given disease

Example: 5 Previously healthy homosexual men (this is the characteristic) were diagnosed to have Pneumocystis carinii pneumonia (this is the disease)

- Advantage of case series: build up a picture of the natural history of a disease

- Both case report and case series can be used to formulate hypothesis
- Disadvantages of case series and case report: no prevalence and incidence (because we don't know about the other cases) and no there is no control group

C- Ecological studies:

- Type of correlational study.
- Description of a relation between a factor and a particular disease, i.e.: describe disease or drug use problems in relation to some factor of interest.
- Use data that has been already collected

- Existing statistics are used to compare the mortality or morbidity experience of one or more populations with some overall index exposure.

Example: Comparing cigarette consumption with rates of cancer, Comparing Alcohol consumption with coronary heart disease mortality

Advantages:

- Quick and cheap to conduct.
- It can generate new hypotheses.
- It can identify new risk factors.

Disadvantages:

- It is unable to control for confounding factors. Correlation but not causation of a risk factor.
- It cannot link exposure with disease in individuals as those with disease may not be exposed.
- Its units of study are populations not individuals. Therefore, does not reflect association at individual level.
- Present only a snapshot of problem.

D- **Cross sectional studies:** **BEST FOR DISEASE BURDEN (prevalence)**

- Type of ~~analytical~~ observational! study which collects information about behaviors among a specific population
- Mainly used for prevalence of a condition, disease, and injuries (aka: prevalence studies)
- Usually used as initial exploration of a hypothesis before conducting a case-control or follow-up study

Advantages: quick (all variables collected at once) estimate prevalence, important in public health for assessing the burden of disease in a specified population and in planning and allocating health resources

Disadvantages & limitations:

- ✈ Not suitable for a disease which is rare or of short duration (more effective in chronic diseases) e.g.: fracture, infection → have to find incidence(by cohort study) (in these cases we)
- ✈ Difficult to separate cause and effect except in exposures which do not change // e.g.: Genetic characteristics such as ABO blood group and HLA so cannot obtain cause-effect

relationship // difficult to separate cause and effect since measurement of exposure and disease at any one point in time = Exposure and outcome are assessed simultaneously

- ✈ Expensive
- ✈ Recall bias
- ✈ Seasonal variations of disease are not well represented
- ✈ Survivors of cohort only
- ✈ No interpretation given by results

تفسير

حجم العينة

- Sample size in cross sectional studies depends on: question, population size and distribution of the condition

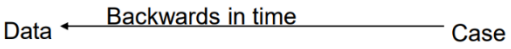
For example: hypothyroidism is common among women aged 50 to 70 but less common amongst men at this age group. Therefore, we need a large sample from men in the general population to get men with hypothyroidism.

2. Analytical

مقارنة مجموعة مع مجموعة أخرى

A. **Case-control studies:**

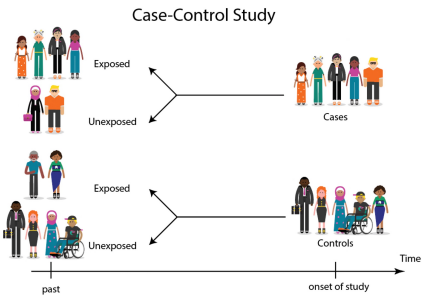
- Group of people with a disease are compared to a group without the disease from the same population
- The purpose of the comparison is to determine whether, in the past, the cases have been exposed more (or less) often to a specific factor than the controls



- Designed to assess association between disease occurrence and exposures (e.g., causative agents, risk factors) suspected of causing or preventing the disease.
- More efficient than a cohort study because a smaller sample size is required.
- The selection of subjects based on disease status vs cohort→ based on exposure.
- Controls are chosen from the same population yielding the cases

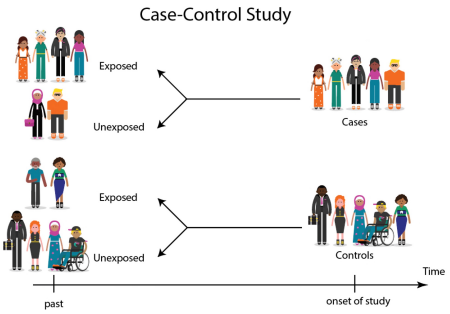
Advantages

- ✈ Able to look at many different possible risk factors (common exposures)
- ✈ Able to study diseases with a long latency period → فترة كمون المدى
- ✈ Useful for the study of rare diseases
- ✈ Relatively quick and inexpensive
- ✈ Odds ratio estimated



SEVERAL RISK FACTORS FOR SINGLE DISEASE

Disadvantages



- ✈ Not suitable for the study of rare exposure (rare risk factors)
- ✈ We cannot be certain that exposure came before disease
- ✈ Cannot measure disease incidence and prevalence
- ✈ Choice of controls difficult
- ✈ Very susceptible to bias (especially selection and recall bias)

Bias: systemic error in an epidemiological study

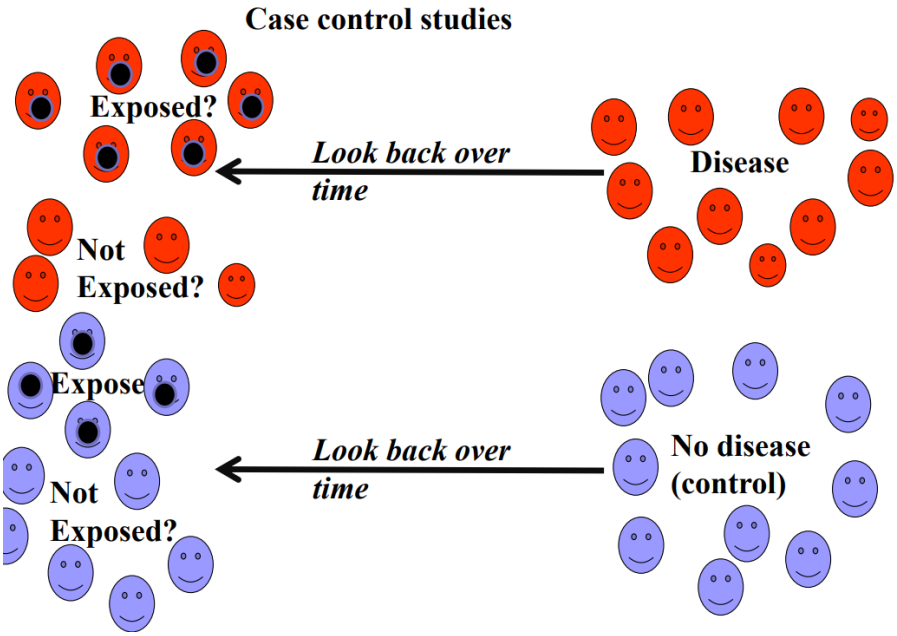
➔ Selection bias: inappropriate controls (so randomization done!)

➔ Observation bias

Subject and recall bias (recollections)

Interviewer bias: blind if possible

Misclassification bias [a systematic error that can occur at any stage in the research process. It occurs when an individual is assigned to a different category than the one to which they should be assigned].



Important steps in designing a case-control study

1. Specify the case definition
2. Control-to-case ratio must not increase beyond 4:1

As the number of controls per case increases, the power of the study also increases

3. Matching of cases and controls - often used in case-control studies to decrease confounding and selection bias
   → A confounding factor is one that is associated with the exposure and that independently affects the risk of developing the outcome, but that is not an intermediate link in the causal chain between the exposure and the outcome under study

Helps to ensure that these groups are similar with respect to important risk factors.

For example, if age and sex are the matching variables, then a 35-year-old male case is matched to a 35 year old male control

- ☐ Pair matching (one to one individual matching)

Disadvantages of matching: time consuming, some cases excluded, discard unmatched.

- Odds ratio used for data analysis

How to calculate odds ratio from case-control study:

$$OR = \frac{\text{Odds of exposure}_{\text{cases}}}{\text{Odds of exposure}_{\text{controls}}}$$

Odds of exposure(cases): number of exposed in cases /number of unexposed in cases
Odds of exposure(control): number of exposed in control /number of unexposed in control

B. **Cohort study people are identified and grouped with respect to whether or not they have been exposed to a specific factor, and then** followed up to determine if the incidence of a particular disease is greater/less compared to the incidence of the non-exposed control group

e.g.: aspirin intake and colorectal cancer, HTN as risk factor for spontaneous intracerebral hemorrhage. Framingham heart study.

* Life expectancy of cerebral palsy children
* Fine needle breast biopsy and breast cancer

BOTH GROUPS FREE FROM DISEASE AT BEGINNING!

Advantages:

BEST observational for establishing cause-effect relationships.

- ✈ The incidence rates of an outcome over time
- ✈ Analyse associations between the rates of the outcomes and risk factors or predictive factors
- ✈ Describe the natural history of disease (BEST)
- ✈ Useful for studying rare exposures → for this purpose

- We can calculate risk ratio or relative risk
- Allows for examination of multiple effects of a single exposure
- Less bias than other studies

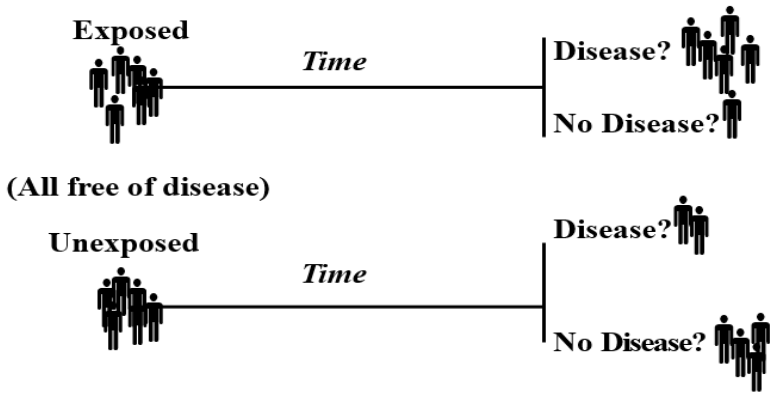
BOTH GROUPS FREE FROM DISEASE AT BEGINNING!

Disadvantages:

- Notefficient for rare disease (since must follow-up very large numbers of patients to pick up one case)
- Large sample
- Drop-out biases (loss during follow-up due to deaths or leaving the study)
- If losses to follow-up are significant during the study, then the validity of the results can be seriously affected
- change in diagnostic methods
- difficult in locating subjects

  Changes in exposure status (such as quitting smoking or employees change job)

  Example: we can by a cohort study to prove that Hypertension as a risk factor for spontaneous intracerebral haemorrhage
- Expensive and takes many years
- Cannot test current hypothesis:



SEVERAL DISEASES FOR SINGLE RISK FACTOR

Types of cohort studies:

A- Birth cohort: all individuals in a certain geographic area born in the same period (usually a year)

B- Inception cohort: individuals with some factors like where they live and work

C- Exposure cohort: individuals with a common exposure (smoking, radiation)

Healthy worker effect: most workers are healthy with a low death rate because the severely ill and disabled is excluded from work

يجب الانتباه لهذا التأثير عند عمل الدراسة

Measurement of exposures should be based on intensity, duration, regularity, and variability

Exposures in cohort may be continuous like smoking) or acute (not repeated in subject's lifetime) or intermittent

Another two types of cohort studies:

A- Open cohort: subjects allowed to enter the study at various times after start of study

B-Closed cohort: no subjects can be added to the study after it has begun.

Another classification:

1- Retrospective cohorts:

Advantages: Information on prior exposure and disease status, all the events in the study have occurred rapid and low cost, mainly for exposures that has been discontinued such as (medical treatment)

Disadvantages: Recall bias

2- Ambi-directional Cohort: Data collected both retrospectively and prospectively (e.g.: data from 5 years ago and then continue follow-up another 30 years.

3- Midpoint analysis: occurs when a defined point in time in the study, all data collected to that point are analyzed so a decision can be made to stop or continue the study.

Nested case-control study: Case-control study within a cohort study

Example: You are following up two groups for a cohort study for smoking and CHD, during follow-up you found 30-40 cases with thyroid cancer which is rare, and you want to study the risk factors for this, so you do case control study on those subjects.

Experimental Designs

Two groups from a population compared for the effect of a particular regimen in contrast to another regimen in the controls (there is human intervention)

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.

- The most definitive tool for evaluation of the applicability of clinical research

Types of intervention(exposures)

- Drugs
- Surgery
- Type of management
- New services

Advantages:

- ✈ Provide stronger evidence of the effect than observational studies (Yield more valid results)
- ✈ No inclusion bias (using blinding)
- ✈ Controlling for possible confounders
- ✈ Comparable Groups (using randomization)
- ✈ Test the effectiveness and safety of an experimental treatments

انحياز من ناحية حين يختار

بدون control vs non-control

Disadvantages: (RCT)

- ✈ Large trials
- ✈ Loss during follow-up
- ✈ Compliance الإلتزام
- ✈ Expensive
- ✈ 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 disadvantage

- Too few patients
- Failed randomization
- Flawed analysis-interpretation
- Power of study: not big enough [**the probability of detecting a difference between study groups when a true difference exists**.]

Clinical trials: التجارب السريرية

Choice of design depends on:

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

Phases of clinical trials:

A- Preclinical: animal studies, pharmacological and biochemical research for toxicity and bioavailability (for example: rabbit serum)

B- Phase I: healthy people, n= (~ 10 - 40)
For metabolism and pharmacologic activities of the drug in humans, side effects, drug effectiveness, and pharmacokinetics of drug

C- Phase II: few very sick patients

For defining the patient's population, effectiveness of the drug, doing ranges and doses, short term side effects, risk of the drug

D- Phase III: Rigorous testing, large randomized controlled, possibly blinded, experiments

For gathering additional information about effectiveness and safety of drug, basis for physician labeling

E- Phase IV: Post-marketing surveillance: مراقبة ما يحدث على المدى البعيد بعد تسويق المنتج
trial of an approved treatment with long-term follow-up of safety and efficacy

- For additional information about efficacy and safety profile of drug
- 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.

Considerations in clinical trials:

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	

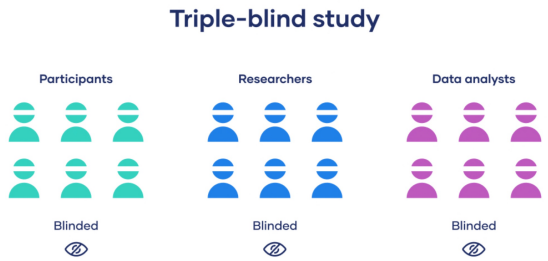
Types of blinding:

1. Open (each one knows his role)
2. Single blind (subjects do not know if he is in the controls or not)
3. Double blind (both investigator and the subject does not know wither the subject is in the control or not)
4. Triple blind (subjects, investigator, data analyser)

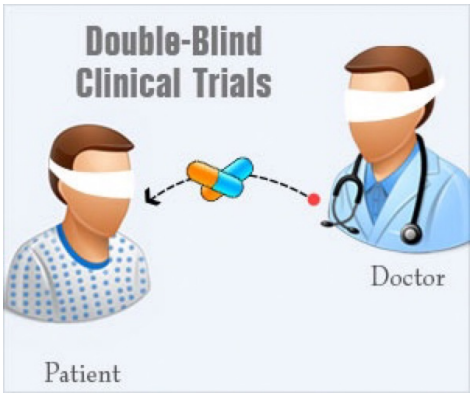
Sometimes blind is difficult (like in fracture injuries and traumas because it's clear for all the three: subjects, investigator, data analyser)

Types of clinical trials:

- Randomised
- Non-randomised
- Single centre
- Multi-centre
- Phase I-IV trials



Randomised controlled clinical trials (GOLD STANDARD)

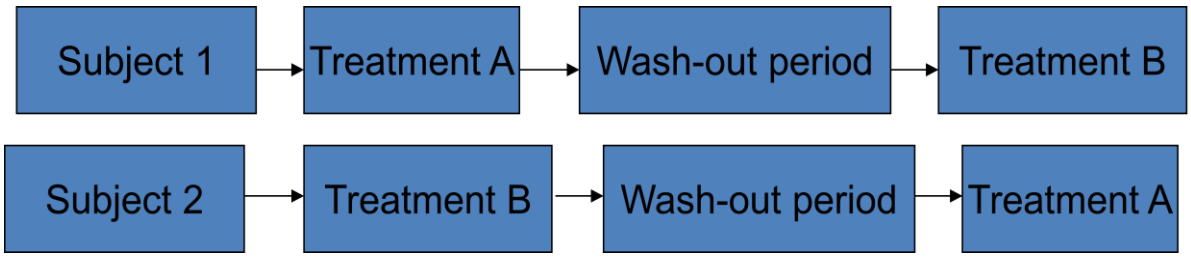


* parallel design
Two diff. treatment at same time + compare
- Headache
- HTN

→ Another design for clinical trials

Cross-over clinical design

Is a type of clinical trial, each patient gets both treatments



Example:

Treatment A and Treatment B (could be placebo)

Half get A then B

Half get B then A

Wash-out period in between: the length of time that someone enrolled in a trial must not receive any treatment before receiving the trial's experimental therapy

Advantages: patient as own control, less variations, much smaller sample size

Requirements: carry over period(s)

Preventive trials:

تجارب وقائية

The same as above but we check the effect of a preventive measure

Advantages: check the effectiveness of an intervention (التدخل الطبي), much controlled by researchers, blinding is more likely no confounding factor due to randomization, a gold standard for epidemiological studies.

Disadvantages: limited because of ethical concerns (مخاوف أخلاقية), greater number of subjects needed since risk of developing disease in people free from disease is small, expensive, difficult to design and control.

Two methods:
A- if the disease is extremely common or extremely severe, the preventive measure applied to a large group:
السعدان الدليمي
e.g., vaccination to prevent whooping cough

vaccination to prevent poliomyelitis

B- if the disease is rare, it's applied to the people with high risk:
e.g., vaccine to prevent Hepatitis B

Community trials:

Interventions studied on a community level note that community may be (a county, state, or school district)

Intervention: Any program or other planned effort designed to produce changes in a target population

May be behavioral intervention, nutritional intervention, a screening intervention

Example: A media campaign aimed at reducing smoking rate, adding fluoride to water to prevent carries.

From revision lecture: Imp

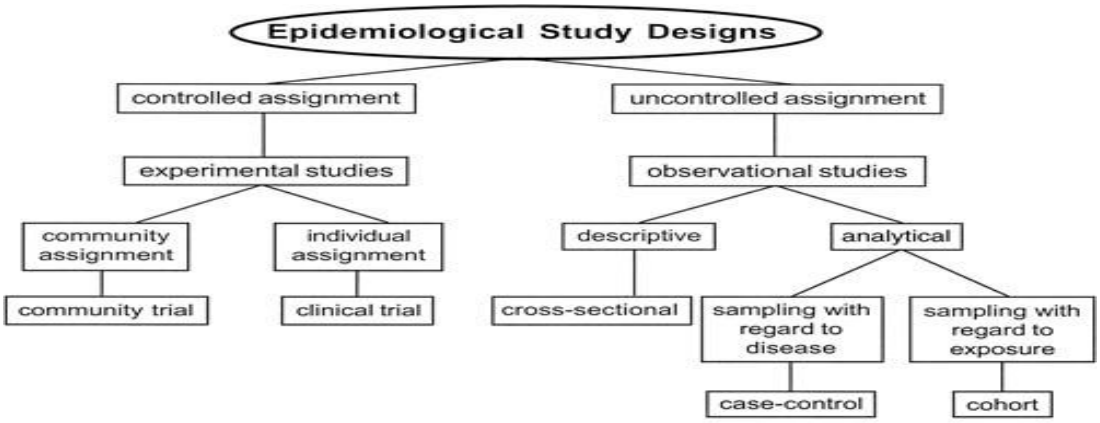
الباحث يتدخل

Controlled assignment, two types: individual trial + community trial → investigator decides + intervenes
(aka= clinical trials)
Uncontrolled assignment: investigator has no control over what is happening and do not intervene [observational + analytical]

e.g.: Aspirin reduces CRC, if uncontrolled, take pharmacy records for patients taking aspirin for other reasons and see if they have reduced CRC risk and compare to controls (people not taking aspirin). Then compare over 10 to 20 years incidence CRC to see if preventive.

Controlled: two groups give one aspirin other no aspirin

Extra notes:



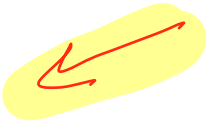
58-In a study of the cause of lung cancer, patients who had the disease were matched with cancer free individuals. The frequency of cigarette smoking was then compared in the two groups. What type of study was this?
Select one:

a. Prospective cohort
b. Cross sectional
c. Experimental
d. Case-control
e. Case series

Causation vs. association
اذا تم التاكد من الاربع نقاط التالية
(احفظهم جيدا)

- Biologic plausibility, Laboratory evidence, Dose-response, Exposure precedes the outcome

EXAMPLES: VIMP



FOR EXAM !

- Case Parkinson incidence 1 in 100000 and want to know risk factors? Case control
- Risk factor for coronary heart disease known and follow-up to know if disease occurs? Cohort study
- Burden of type 2 DM in karak (prevalence)? Cross-sectional study
- Studied and presented a group of cases? Case series
- Meat consumption correlated with incidence of colorectal cancer? Ecological study (correlation of a certain factor with incidence of disease)

حديث أبي عبد الرحمن عبد الله بن مسعود قال: سألت النبي ﷺ أي العمل أحب إلى الله تعالى؟ قال: الصلاة على وقتها، وقال: قلت: ثم أي؟ قال: بر الوالدين، قلت: ثم أي؟ قال: الجهاد في سبيل الله. متفق عليه ☪☼

By: Nadine Absy. Please make duaa' for my grandmother sitto yasmeena ربنا يرحمها

Summary for phases of clinical trials

	Phase 0	Phase 1	Phase 2	Phase 3	Phase 4
لمن يعطى الدواء	Animal	Healthy Person نعطي جرعة قليلة لمريض واحد ثم نزيد الجرعة وعدد الأشخاص	Few very sick patients	300 – 1000 patient	يطرح الدواء في السوق ويستخدم من قبل المجتمع
الهدف من المرحلة	Determine toxicity & bioavailability	• Metabolism and pharmacologic in human • Side effects with increase dose • Early evidence on effectiveness	• If the drug benefits patients in the population • Evaluate effectiveness • Determine dosing range • Common short term side effects • Risks associated with drug	• Gather information effectiveness and safety • Basis of physician labeling	• Learn more about efficacy and safety • Study new race and age group • Long term adverse effects
إجراءات خاصة		Dose escalation to reach Maximum Tailored dose (MTD)		Large randomized controlled, blinded experiments	Long term follow-up