- **Why do research studies?**

- To collect data on usual and unusual events, conditions and population groups.
- To test hypotheses formulated from observations and/or intuition
- Ultimately, to understand better one's world and make "sense of it".

Epidemiology:

The study of the distribution of a disease or condition in a population and the factors that influence that distribution.

- **Classifications of research studies:**

i- Observational Studies:

- Groups are studied and contrasts made b/w groups.
- The observed data collected are analyzed

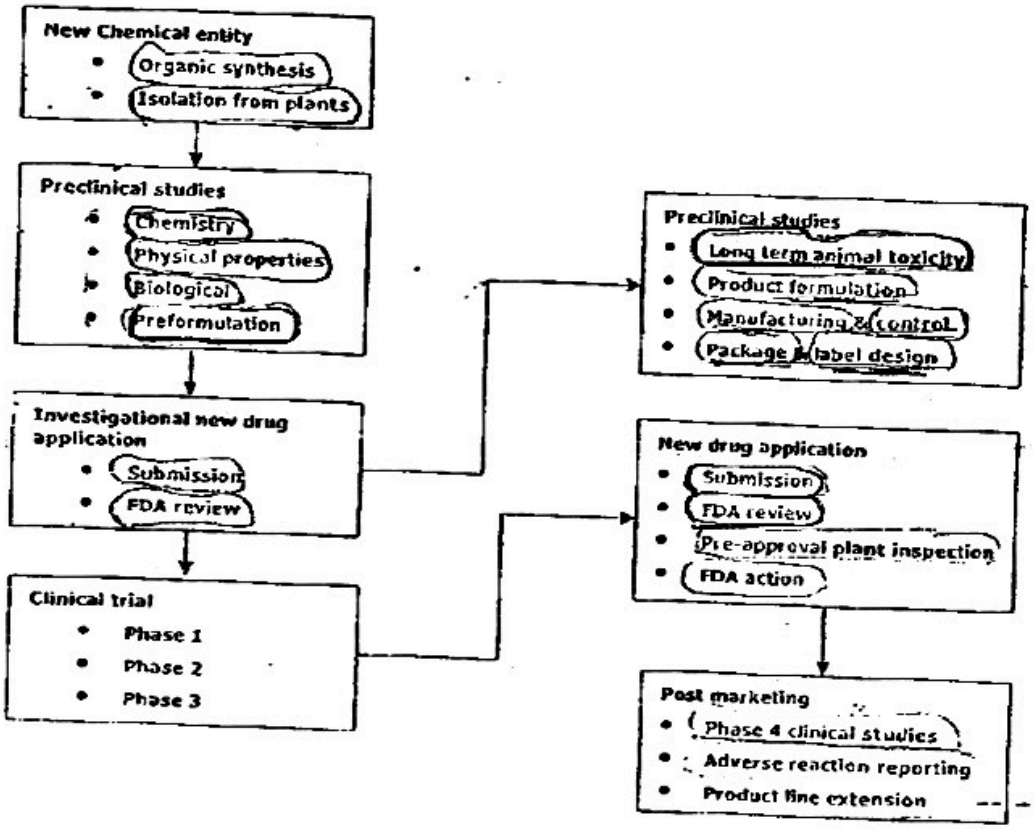
ii. Analytic Studies:

- Also called experimental
- Study the impact of a certain therapy
- ultimately the investigator controls factor being studied.

iii. Clinical Trial:

- Considered the "true" experimental study
- "Gold Standard" of clinical research
- Often a prospective study that compares the effect and value of an intervention against a control in human subjects

Steps involved in clinical trial:



5M

- Preclinical Studies:

- Choice of animal model:

- Typically, in drug development studies animal testing involves two species.

The most commonly used models are murine and canines, although primate and procaine are also used.

- The choice of species is based on which

will give the best correlation to human trial.

- Difference in the gut, enzyme activity, circulatory system or other consideration make certain models more appropriate based on the dosage form, site of activity, or noxious metabolite.

- Acute toxicity:

Acute toxicity studies are required for all drugs. These studies involve single administration of the agent up to the lethal level in at least two species, one rodent and one non rodent.

Sub acute and chronic toxicity:

These studies are required for most agent especially those intended for chronic use. Tests are usually carried out for at least

the amt of time proposed for human applications ie. 2-4 weeks (sub acute) or 6-24 month (chronic) in at least two species.

Types of animal testing:

- Pharmacological profile
- Teratogens
- Mutagenesis
- Carcinogenesis

- Based on pre-clinical trial, No observable effect level (NOEL) on drug are established, which are used to determine initial phase 1 clinical trial dosage levels on a mass API per mass patient basis.

- Pre clinical studies involve in vitro (test tube) and in vivo (animal or cell culture)

experiment using wide ranging dose of the study to obtain preliminary efficacy, toxicity, and pharmacokinetic information.

- Such test assists pharmaceutical companies to decide whether a drug candidate has scientific merit for further development as an investigational new drug.
- Each class of product may undergo different type of preclinical research. For instance, drugs may undergo pharmacodynamics (PD), pharmacokinetic (PK), ADME and toxicity testing through animal testing.
- This data allows researcher to estimate a safe starting dose of the drug for clinical trials in human.
- Studies of drug's toxicity includ which organ are targeted by the drug.

• Types of clinical trials: 2m

The U.S. National institutes of Health (NIH) organize trials into 5 different types:

1. Prevention trials:

- Look for better way to prevent disease in people who have never had the disease or to prevent a disease from returning.
- This approach may include medicine, vitamin, vaccines, minerals or life style changes.

2. Screening trial:

Test the best way to detect certain disease or health condition.

3. Diagnostic trials:

Conducted to find better test or procedure for diagnosing a particular disease or condition.

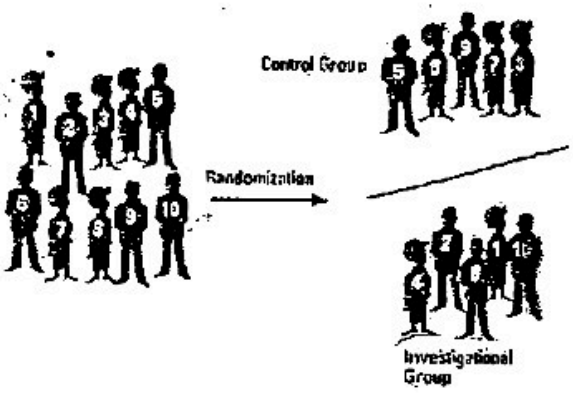
4. Treatment trials: test experimental treatment, new combination of drugs, or new approaches to surgery or radiation therapy

5. Quality of life trials: explore way to improve comfort and the quality of life for individual with a chronic illness.

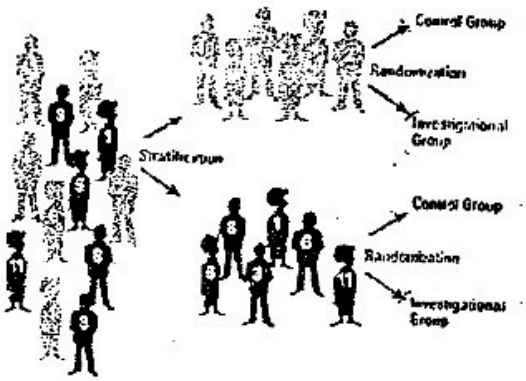
□ Clinical Trial Study Design: 5M

- Randomized
- Non-randomized
- Blinded: Participants do not know if in experimental or control group
- Double blinded: Participants and staff do not know group assignment
- Placebo: inactive pill with no therapeutic value

Randomization



Stratification



- Clinical trial protocol: 5M

- The protocol describes the scientific, objective, design, methodology, statistical consideration and organization of the planned trial.

- Detail of the trial is also provided in other documents referenced in the protocol such as investigator's brochure.

- The protocol contains a precise study plan for executing the clinical trial, not only to assure safety and health of the trial subjects, but also to provide an exact template for trial conduct by investigators at multiple locations (in a multicenter trial) to perform the study in exactly the same way

- The protocol also gives the study administrator (often a contract research organisation) as well as the site team of physicians, nurses and clinic administrator a common reference document for site responsibilities during the trial.

- The format and content of clinical trial protocols sponsored by pharmaceutical, biotechnology or medical device companies in the United States, European Union, or

Japan has been standardized to follow Good Clinical Practice guidance issued by the international conference on Harmonization of Technical Requirement for registration of pharmaceutical for Human Use (ICH).

- Regulatory authorities in Canada and Australia also follow ICH guideline.

- Components of clinical Trial Protocols:

- Investigating two or more conditions so have two (+) groups

  -Ex: drug vs. placebo; medicine vs surgery

- Specific inclusion/exclusion criteria

- Sample size and power calculations

- Study participant recruitment:

  - Identify eligible participants

  - Explain study

- Provide informed consent
- Reassess eligibility
- Assign to one group

- Participants should be told:
  - May have side effects (adverse effects)
  - Time commitment
  - Benefits and risks
  - May withdraw at any time
  - Enrollment 100% voluntary

- Design feature:

1. Informed consent: informed consent is a legally-defined praess of a person being told about key facts involved in a clinical trial before deciding whether or not to participate.
  - The research team provides an informed consent document that include trial details,

such as its purpose, duration, required procedures, risks, potential benefits and key contacts. The participant then decides whether or not to sign the document in agreement.

- Informed consent is not an immutable contract, as the participant can withdraw at any time without penalty.

2. Statistical power:

The Sponsor's goal usually is to obtain a statistically significant result showing a significant difference in outcome b/w the groups of patients who receive the study treatment. The number of patient enrolled in study has a large bearing on the ability of the study to reliably detect the size of the effect of the study intervention.

This is describing as a power of the trial. The larger the sample size or number of participants in the trial, the greater the statistical power.

3. Administration:

Clinical trials designed by a local investigator and federally funded clinical trials are almost always administered by the researcher who designed the study and applied for the grant. Phase 3 and phase 4 clinical trial of new drugs are usually administered by a contract research organisation (CRO) hired by the sponsoring company.

A CRO is a company that is contracted to perform all the administrative work on a clinical trial. It recruits participating researchers, train them, provide them with supplies, coordinates

Study administration and data collection, set up meetings, monitors the sites for compliance with the clinical protocol and ensures that the sponsor receives clean data from every site.

4. Ethical conduct:

All studies that involve medical or therapeutic intervention on patients must be approved by a supervising ethics committee before permission is granted to run the trial.

- In the U.S., this body is called the Institutional Review Board (IRB).
- ICH GCP is set of standard used internationally for the conduct of clinical trials. The guideline aim to ensure that the right, safety and well being of trial subjects are protected.

5. Sponser:

-Sponsor is responsible for:

Accurately informing the local site investigator of true historical safety record of drug, device or other medical treatment to be tested and of any potential interaction of the study treatment with already approved medical treatment, monitoring the results of the study as they come in from the various site, as the trial proceeds, collecting adverse event reports from all site investigators in the study, and for informing all the investigators of the sponsor's judgment as to whether these adverse events were related or not related to the study treatment. The sponsor and the local site investigators are jointly responsible for writing a site specific informed consent that accurately inform the

potential subjects of the true risks and potential benefits of participating in the study.

6. local site investigators:

If a physician investigator believes that study treatment may be harming subject in the study, the investigator can stop participating at any time.

- The local investigator is responsible for:

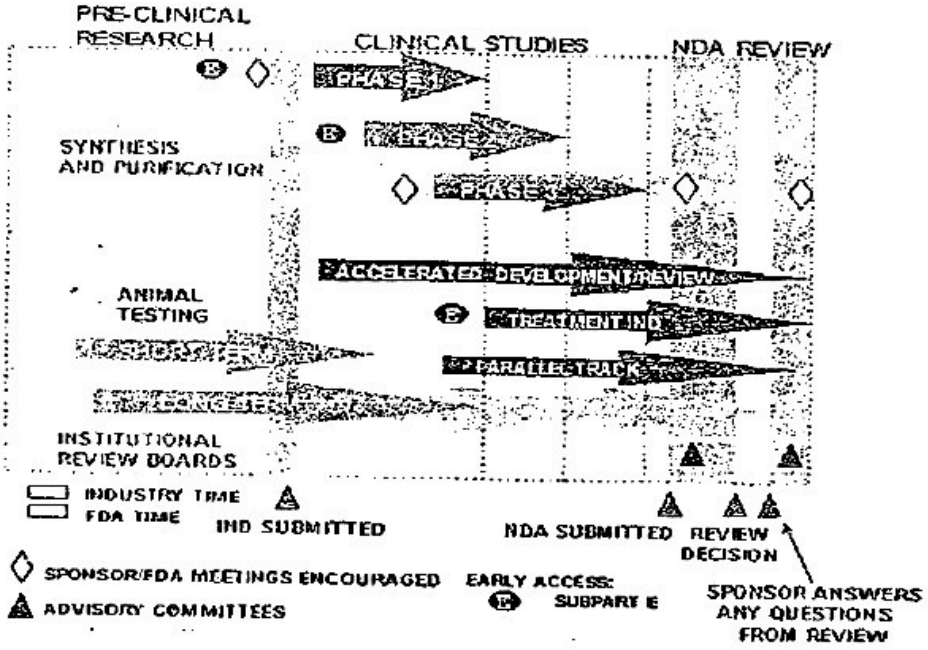
- Conducting the study according to the study staff throughout the duration of the study
- Ensuring that potential subjects in the study understand the risk and potential benefit of participating in the study.
- Reviewing all adverse event reports sent by the sponsor.
- Being truthful to the local IRB in all

Communication relating to the study.

- The drug development and approval process:

1. Early research and preclinical testing
2. IND application filed with FDA
3. Clinical trials (phases 1, 2, and 3)
4. NDA filed with FDA
5. FDA validates claim and approves drug

Phases of Clinical Product Development



Various phase in clinical trials:

	phase1	*Phase 2*	*Phase 3*	*phase4*
objective	Determine the metabolic& pharmacological action & the maximally tolerated dose.	Evaluate effectiveness, determine the short term side effect & identify common risk for specific risks for a specific population & disease.	Obtain additional information about the effectiveness in clinical outcomes & evaluate the overall risk benefit ratio in demographically diverse sample.	Monitor ongoing safety in large population & identify additional uses of the agent that might be approved by FDA.

Phases of clinical Trials:

Phase 1:

- 15-30 people
- What dosage is safe?
- How should treatment be given?
- How does treatment affect the body?
- Initial administration of drug to humans
- Assessment of human toxicology
- Determine Maximum Tolerated Dose (MTD)

or optimal Biological Dose (OBD)

Phase 2:

- Less than 100 people
- Begin if phase 1 studies do not reveal unacceptable toxicity.
- Primarily focus on collection of preliminary data on whether the drug has effect in a defined patient population
- The relationship between dose and effectiveness
- Continue to evaluate safety and short-term side effects.
- For controlled trials, patients receiving the drug are compared with similar patients receiving a different treatment, usually a placebo or a different drug questions asked:

Does treatment do what it is supposed to?

How does treatment affect the body?

Phase 3:

- From 100 to thousands of people
- Compare new treatment with current standard
- Begin if preliminary evidence of effectiveness is shown during phase 2.
- Gather more information about safety and effectiveness in a defined population.
- May form the primary basis of an efficacy claim

Post marketing surveillance phase 4:

- From hundreds to thousands of people
- Usually takes place after drug is approved
- Used to further evaluate long-term safety and effectiveness of new treatment.

- Methods involved in post marketing surveillance:

non-experimental studies (observational)

1. Descriptive non experimental studies

   A. Case reports

   B. Case series

2. Analytical non-experimental studies

   A. Case control

   B. Cohort study

   C. Cross sectional study

A. Case Control:

- By definition, a case control study involves two population - case and control.
- In this study, cases and controls must be comparable with respect to known 'confounding factors' such as age, sex, occupation, social status.

• For example. the link b/w use of oral contraceptive and occurrence of ovarian cysts in women of child bearing can be conducted. Here prior use of oral contraceptive in the age group can be selected as the cases.

• The controls are those without the prior use of oral contraceptives.

• In case control, matching is important.

• Case control studies are used when outcomes and exposure to the drug are rare.

• The case control studies are widely used to assess the safety of medicines.

• Ex of association b/w the drugs and adverse events:

- NSAIDs and peptic ulcer
- Oral contraceptives and venous thromboembolism

• Data from case control studies are used to

calculate an odd ratio, which is the ratio of the odds of developing the disease for exposed patient to the odds of developing the disease for un-exposed patients.

The basic design of a case control study is

Suspected or Risk factors	Cases (disease present)	Control (disease absent)
present	a	B
absent	c	D
	a+c	b+d

- To illustrate, if it is our intention to test the hypothesis that cigarette smoking causes lung cancer, using the case control method, the investigation begins by assembling, a group of lung cancer cases (a+c) and a group of suitably matched control (b+d)
- One then explores the past history of these two groups for the presence or absence of smoking, which is suspected to be related

to the occurence of the lung cancer.

- If frequency of smoking, a/(a+c) higher in cases than in controls, b/(b+d), an association is said to exist b/w smoking and lung cancer.

Advantages:

1. Relatively easy to carry out
2. Rapid and inexpensive
3. Require comparatively few subjects
4. No risk to subjects
5. Allows the study of several different etiological factors (eg: smoking, physical activity and personality characteristics in myocardial infarction).
6. Ethical problems minimal

Disadvantages:

1. Problems of bias relies on memory or past records.

2. Selection of an appropriate control group may be difficult.

3. We cannot measure incidence and can only estimate the relative risk.

4. Not suited to the evaluation of therapy or prophylaxis of disease.

b. Cohort Study:

Cohort Study are Studies that identify subsets of a define population and follow them over time, looking for differences in their outcome.

- Cohort studies generally are used to compare exposed patients to unexposed patients, although they can also be used to compare one exposure to another.
- The term "cohort" is defined as the group of people who share a common characte-

ristic or experience within the defined time period eg. Age, occupation, exposure to a drug or vaccine, pregnancy, ensured person.

Indication for cohort studies:

a. When there is good evidence of an association b/w an exposure and disease as derived from clinical observations and supported by descriptive and case control studies.

b. When exposure is rare, but the incidence of disease high among exposed e.g: special exposure groups like those in industries, exposure to X-ray.

c- When attrition of study population can be minimized e.g. follow up is easy, cohort is stable, cooperative easily accessible.

d. When ample funds are available.

Framework of a cohort study

- The basic design of a simple cohort study is shown. We begin with a group of cohort (a+b) exposed to a particular factor thought to be related to disease occurrence, and a group (c+d) not exposed to that particular factor. The former is known as study cohort, and the latter control cohort.

cohort	yes	no	total
Exposed to putative etiologic factor	a	b	a+b
Not exposed to putative etiologic factor	c	d	C+d

• Types of cohort study:

1. Prospective cohort study
2. Retrospective cohort study
3. Combination of retrospective and prospective cohort study.

1. Prospective cohort study:

A prospective cohort study or current cohort study is one in which the outcome (e.g Disease) has not yet occured at the time the

investigation begins.

- Most prospective studies begin in the present and continue into future.
- For eg: The long term effects of exposure to uranium was evaluated by identifying a group of uranium miners and a comparison group of individual not exposed to uranium mine and by assessing subsequent development of lung cancer in both the groups.

2. Retrospective Cohort Studies:

A retrospective cohort study or historical cohort study is one in which the outcomes have all occurred before the start of the investigation.

- The investigator goes back in time, sometimes 10 to 30 years, to select his study groups from existing records of past employment,

medical or other records and traces them forward through time, from a past date fixed on the records, usually up to the present.

3. Combination of retrospective and prospective cohort studies:

In this type of study, the retrospective and prosp-ective elements are combined.

- The cohort is identified from the past records, and is assessed of date for the outcome; the same cohort is followed up prospectively in to future assessment of outcome.

- Cohort study example:

- The news's health study followed more than 160,000 American nurses over time, starting in 1976. the exposure of interest was oral contraceptive use.

o The researcher on that project were able to prospectively examine different outcomes such as cancers (i.e breast, colon, skin), deaths, thromboembolism and skeletal problems.

o Advantages:

- Incidence can be calculated.
- Several possible outcomes related to exposure can be studied simultaneously.
- It provide direct estimate of relative risk
- Dose response ratio can also be calculated.

Disadvantages:

- Studies involve a large no. of people.
- It takes a long time to complete the study.

- Certain administrative problems such as loss of experienced staff, loss of funding.
- There may be changes in the standard methods or diagnostic criteria of the disease over prolonged follow-up.
- The study itself may alter people's behavior
- Expensive

C- Cross-Sectional Study:

- Cross sectional study may be of descriptive or analytical nature.
- Cross sectional study are also known as instantaneous studies, simultaneous studies or prevalence studies.
- There are studies of use of drugs at the specific point of time and are conducted through surveys, data base analysis or

medication chart reviews.

- They help the collection of data on a cross section of population, which may comprise the whole population or a population (sample) of it.
- This type of studies provides information about the situation that exists at a single time.

Advantages:

- The studies can be short term.
- Relatively inexpensive to conduct.
- It can only measure disease prevalence rather than incidence.

Disadvantages:

- No direct estimate of risk and the slope for bias. Since exposure and disease are measure at the same point of time.

- It is not possible to establish temporality, that is, whether the exposure or presence of a characteristic preceded the development of the disease or condition.

MAIN DIFFERENCE BETWEEN CASE CONTROL AND COHORT STUDI

CASE CONTROL STUDY	COHORT STUDY
1) Proceeds from effect to cause.	1) Proceeds from cause to effect
2) Starts with the disease.	2) Starts with people exposed to risk factor or suspected cause.
3) Tests whether the suspected cause occurs more frequently in those with the disease than among those without the disease.	3) Tests whether disease occurs more frequently in those expose than in those not similarly exposed.
4) Usually the first approach to the testing of hypothesis, but also useful for exploratory study.	4) Reserve for testing of precisel formulated hypothesis.
5)Involves fewer No .of subjects	5)Involves larger No .of subjects
6)Yields relatively quick results	6)Long follow up period often needed involving delayed result
7)Suitable for study of rare disease	7)Inappropriate when the disease or exposure under investigation is rare
8)Generally yields only estimate of RR(odds ratio)	8)Yields incidence rates, RR as we as AR
9) Cannot yield the information about disease other than selected for study	9) Can yield the information about more than one disease outcome
10)Relatively inexpensive	10)expensive

-The Final Step: FDA approval

- Review of New Drug Application (NDA) or

Biologics' Licence Application (BLA)

- Labeling
- Continued monitoring
- Feedback

- Releasing the results of clinical trials:
  - Peer-reviewed journals
  - Public announcements
  - Results not made public until end of trial.