PHARMACOEPIDEMIOLOGY & PHARMACOECONOMICS

SHORT ANSWERS 02 MARKS

1. **Define prevalence**.

   Prevalence refers to the total number of individuals in a population who have a disease or health condition at a specific period of time, usually expressed as a percentage of the population. Prevalence can also be measured over a period of time (e.g. a year). This second type of prevalence is called period prevalence ; it is a combination of point prevalence and incidence.

   FORMULA : existing cases/ population at risk = during specific period of time.

2. **What is signal generation. Explain its significance.**
   The term signal is widely used in electronics for many years . it was coined in ADR reporting and pharmacovigilance in recent times with the evolvement of ADR monitoring system at global level with support of WHO. It is used as an early warning in the case of ADRs. Signal is a reported information on a possible causal relationship between an adverse event and a drug or medicine. Eg; aspirin 1st indicated for pain & inflamation later it is used for in cardiac disease bcoz of its blood thinning property.

   Signal generation is process by which one gets immediate response to a drug at the earliest . This is very important because it helps one in detecting unexpected side effects to a given drug. If released without it, it could lead to harmful health effects to the users, and may even prove fatal. In case the surveillance shows one suspicious results, this is followed up by investigation to look into the matter and rectify it.

3. **What is outcome research.**
   Outcome assessment (health care) is defined as: research aimed at assessing the quality and effectiveness of health care as measured by the attainment of a specified end result or outcome. Measures include parameters such as improved health, lowered morbidity or mortality, and improvement of abnormal states (such as elevated blood pressure).

4. **Name four computerized databases used for pharmacoepidemiological research.**
   -Institutionalized medical records and databases from hospital and pharmacy claims.
   —System wide databases from health insurance claims or pharmaceutical organization.
   —National databases like Medical Expenditure Panel Survey, National Ambulatory Medical Care Survey.
   —Field data like records from dispensers, sellers or distributers or from small groups.
   —Experimental clinical trial data.

5. **What is willingness to pay.**
   willingness to pay (**WTP**) as a method of measuring **benefits** from healthcare providers. ... The conclusion of this study is that this technique holds promise as a method that can generate monetary values for program **benefits** for future use in **CBA**.

The basic measurement goal is to quantify the trade-offs that consumers are willing to make between reduced health risk and money. Specifically, to identify the maximum **willingness to pay** (**WTP**) for health **benefits**.

6. **Mention the limitations of pharmacoeconomic study.**
   Limitations of Pharmacoeconomic evaluation include a) Sometimes choice of the drugs is given according to the availability. b) Drugs are prescribed under promotional pressurizing activities of marketing executives of pharmaceutical firms. c) For chronic diseases, bio-availability consideration can have an upper hand over Pharmacoeconomics.

7. **What is case series.**
   case series as – a collection of patients with common characteristics used to describe some clinical, pathophysiological or operational aspects of a disease, treatment or diagnostic procedures [2]. Case series is an observational, descriptive research design. It is most useful for describing the potential effectiveness of new interventions, for describing the effectiveness of interventions on unusual diagnoses, and for describing unusual responses (either good or bad) to interventions. Case series can be conducted retrospectively or prospectively.

8. **Define sensitivity analysis.**
   The Sensitivity Analysis (SA) is a method that measures how the impact of uncertainties of one or more input variables can lead to uncertainties on the output variables. Sensitivity analysis is an essential part of every risk assessment, quantitative and qualitative. The gaps in our knowledge are bridged by assumptions, probability distributions, expert opinion, best guesses, and a variety of other techniques. Sensitivity analysis is a systematic investigation of the means by which assessors bridge these uncertainty gaps.

9. **Define attributable risk.**
   Attributable Risk(AR) (sometimes called *Attributable Proportion* or *Attributable Fraction*) is a measure of the prevalence of a condition or disease. Given a group of people exposed to a risk, it's the fraction who develop a disease or condition. Put another way, AR is the cases that would be eliminated if the exposure were also eliminated

$$Attributable\ Proportion = \frac{RD}{CI_e} = \frac{CI_e - CI_u}{CI_e}$$

Where:

- RD = Risk Difference (also called Absolute Risk Reduction)
- CI_e = Cumulative Incidence in Exposed group
- CI_u = Cumulative Incidence in Unexposed group

10. **Define pharmacoeconomics**
    Pharmacoeconomics can be defined as the branch of economics that uses cost-benefit, cost-effectiveness, cost-minimization, cost-of-illness and cost-utility analyses to compare pharmaceutical

products and treatment strategies. Economic evaluations provide healthcare decision-makers with valuable information, allowing optimal allocation of limited resources.
Pharmacoeconomics focuses on the costs and benefits of drug therapy and pharmacoeconomic evaluations provide a basis for resource allocation and utilization.

11. Define spontaneous reporting systems.

Spontaneous Reporting is defined as "A system whereby case reports of adverse drug events are voluntarily submitted by health professionals and pharmaceutical companies to the national pharmacovigilance centre.

THE SPONTANEOUS REPORTING SYSTEM

Passive surveillance system: Health professionals are encouraged to report adverse reactions which they believe to be drug-related directly to

the regulatory authority or

the company marketing the suspected product on a voluntary basis

The spontaneous reporting system process 1. Data acquisition which depends largely on the input of information derived from reports submitted by the health professionals who have encountered what they suspect is an ADR The spontaneous reporting system 1.data acquisition 2.data assessment 3.data interpretation

12. What is QALY and QOL

The quality-adjusted life-year (QALY) is a measure of the value of health outcomes. Since health is a function of length of life and quality of life, the QALY was developed as an attempt to combine the value of these attributes into a single index number.

Quality of life (QOL) is a broad multidimensional concept that usually includes subjective evaluations of both positive and negative aspects of life.

13. Give advantages of Cohort study.

- Can often show temporality of relationship
- Less bias due to prospective evaluation of exposures
- Can evaluate multiple diseases
- can establish cause - effect
- good when exposure is rare
- We can find out incidence rate and Relative risk

Disadvantages of Prospective Cohort Studies

1. You may have to follow large numbers of subjects for a long time.
2. They can be very expensive and time consuming.
3. They are not good for rare diseases.
4. They are not good for diseases with a long latency.
5. Differential loss to follow up can introduce bias.

Disadvantages of Retrospective Cohort Studies

1. As with prospective cohort studies, they are not good for very rare diseases.
2. If one uses records that were not designed for the study, the available data may be of poor quality.
3. There is frequently an absence of data on potential confounding factors if the data was recorded in the past.
4. It may be difficult to identify an appropriate exposed cohort and an appropriate comparison group.
5. Differential losses to follow up can also bias retrospective cohort studies.

14. What is ICER and ACER.

    The incremental cost-effectiveness ratio (**ICER**) is a statistic used in cost-effectiveness analysis to summarise the cost-effectiveness of a health care intervention. It is defined by the difference in cost between two possible interventions, divided by the difference in their effect/ benefits.

    An ACER represents the total cost of a program or treatment alternative divided by its clinical outcome to yield a ratio representing the dollar cost per specific clinical outcome gained, independent of comparators. Average cost effectiveness (ACER) = Net Cost / Net Health Benefit

15. List meta analysis models.

    Fixed effects **model**.
    Random effects **model**.
    IVhet **model**.
    Quality effects **model**.
    Bayesian framework.
    Frequentist multivariate framework.
    Generalized pairwise modelling framework.
    Tailored **meta-analysis**.

16. Define incidence.

    Incidence refers to the number of individuals who develop a specific disease or experience a specific health-related event during a particular time period (such as a month or year).

Incidence proportion (risk)

Number of new cases of disease or injury during specified period /Size of population at start of period

17. Define “Defined daily dose”and “Prescribe daily dose”.

    Defined Daily Dose (DDD): The assumed average maintenance dose per day for a drug used for its main indication in adults.

By applying DDD it is possible to:

- Examine changes in drug utilization over time
- Make international comparisons
- Evaluate the effect of an intervention on drug use
- Document the relative therapy intensity with various groups of drugs

- Follow the changes in the use of a class of drugs
- Evaluate regulatory effects and effects of interventions on prescribing patterns.

The prescribed daily dose (PDD) is defined as **the average dose prescribed according to a representative sample of prescriptions**. The PDD can be determined from studies of prescriptions, medical or pharmacy records, and it is important to relate the PDD to the diagnosis on which the drug is used

18. Give examples of intangible cost involved in pharmacoeconomic study.
Intangible costs • Costs of pain, worry and other suffering which a patient or his family might suffer

19. Define monetary units.
The monetary units for drug use measures are done by pharmaco economic studies. They are cost-effective analysis, cost-benefit analysis, cost- minimization analysis, and cost-utility analysis. Cost-effectiveness analysis evaluates multiple drug treatments for the same condition. The cost of the drug treatments are weighed against the effectiveness of the drug.

20. Explain confounding.
Confounding is the distortion of the association between an exposure and health outcome by an extraneous, third variable called a confounder. Since the exposure of interest is rarely the only factor that differs between exposed and unexposed groups, and that also affects the health outcome or disease frequency, confounding is a common occurrence in etiologic studies.

21. What is record linkage system.
Record linkage is the process of bringing together two or more records relating to the same individual (person),family or entity (e.g. event, object, geography, business etc).• To find syntactically distinct data entries that refer to the same entity in two or more input files.• Part of the data cleaning process, which is a crucial first step in the knowledge discovery process .

22. Give the applications of cost benefit analysis.
APPLICATIONS OF CBA • The overall concept is simple. • CBA can be employed in macro level for policy makers on health care program. • The cost of two alternative treatment can be compared. • Nation wide immunization program can be subjected without difficulty. • It's the best method to study the document value of an existing healthcare services . • It can also be used to evaluate the health care program. • Its used to assess the money value of the large private and public sector projects.

23. List out steps involved in creating a study design for pharmacoeconomic study.
A well-designed pharmacoeconomic analysis involves 10 steps: (1) defining the problem, (2) determining the study's perspective, (3) determining the alternatives and outcomes, (4) selecting the appropriate pharmacoeconomic method, (5) placing monetary values on the outcomes, (6) identifying study resources, (7) establishing the probabilities of the outcomes, (8) applying decision analysis, (9) discounting costs or performing a sensitivity or incremental cost analysis, and (10) presenting the results, along with any limitations of the study. By adhering to the analytic steps described, the

pharmacist undertaking a pharmacoeconomic evaluation has the greatest likelihood of obtaining valid and useful results.

24. What are ad-hoc data sources.

DIFFERENT KINDS OF DATA SOURCES:

1. Spontaneous reporting
2. Global drug Surveillance
3. Case-Control Surveillance
4. Prescription-Event Monitoring

25. Explain selection bias.

Selection bias

occurs when individuals or groups in a study differ systematically from the population of interest leading to a systematic error in an association or outcome.

26. What is case report. What are limitations.

The case report is a specific type of research design that reports on an aspect of the management of one or two patients. It is the first piece of research writing in the health field and represents the most basic type of study design.

Case reports have certain limitations as inherent properties of the design itself and include the following :

regarded as low-level evidence as the observations may be subject to bias.
lacks generalizability.
lacks denominator data that are necessary to calculate the rate of disease.
lacks a comparison or control group to compare outcomes and have little statistical validity.
often describe highly select individuals who may not represent the general population. Since the care rendered to one patient may not produce a similar change in another patient, case reports should not be generalized but for the patient reported.
infrequently cited, and therefore, publishing case reports are likely to decrease the journal's impact factor. This has led many editors to remove case report sections from their journals.

27. What is opportunity cost.

Opportunity costs represent the potential benefits an individual, healthcare provider or hospital *misses out on* when choosing one alternative over another.

- Opportunity cost is the forgone benefit that would have been derived by an option not chosen.
- To properly evaluate opportunity costs, the costs and benefits of every option available must be considered and weighed against the others.
- Considering the value of opportunity costs can guide individuals and organizations to more profitable decision-making.

28. What is the need of post marketing surveillance.

Postmarketing surveillance refers to the process of **monitoring** the safety of drugs once they reach the **market**, **after** the successful completion of clinical trials. The primary purpose for conducting **postmarketing surveillance** is to identify previously unrecognized adverse effects as well as positive effects.

29. Define relative risk?

Relative risk is a ratio of the probability of an event occurring in the exposed group versus the probability of the event occurring in the non-exposed group. For example, the relative risk of developing lung cancer (event) in smokers (exposed group) versus non-smokers (non-exposed group) would be the probability of developing lung cancer for smokers divided by the probability of developing lung cancer for nonsmokers.

Relative Risk = (Probability of event in exposed group) / (Probability of event in not exposed group)

30. Define time risk relationship?

The outcome of an exposure to a drug is related to the time. • It is also true with risks associated with medicines. • There is always a time related association of risk in pharmacoepidemiology. • Certain events like anaphylactic reactions happen immediately after taking an injection while certain other risk events occur after days or months or even years. .Eg: prazosin , an alpha blocker has main effect in dilation of veins and arteries which leads to reduction in BP. It is sometimes also used for BPH. To minimize the impact of first dose effect, prazosin is normally taken at bedtime.

31. Define odds ratio?

It is a measure of association between an exposure and an outcome like Risk Ratio (RR). • Odds Ratio in statistics and epidemiology is commonly abbreviated as 'OR'. • Like Risk Ratio determines probabilities, in OR Odds are used. • In clinical studies and many other settings, the first parameter of greatest interest is the RR and the next one is OR.

32. Define Cost Conequences

Cost consequences analysis (CCA)

This is a form of economic evaluation in which the outcomes (of which a variety of measures are normally presented) are reported separately from costs.

Cost-consequence analysis presents the costs and consequences of numerous intercessions and the results are declared in a disconnected method and are not combined with costs. CCA is comparable to CEA in that results chosen are calculated in a natural unit of effect.

33. What is bias? Explain its different types?

bias is defined as 'an error in the conception and design of a study – or in the collection, analysis, interpretation, reporting, publication, or review or data – leading to results or conclusions that are systematically (as opposed to randomly) different from truth.

Three types of bias can be distinguished: information **bias**, selection **bias**, and confounding.

34. Write a note on VAERS?

Vaccine Adverse Event Reporting System (**VAERS**): VAERS is a program created as an outgrowth of the National Childhood Vaccine Injury Act of 1986 (NCVIA) and is administered by the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC). VAERS accepts reports of adverse events that may be associated with U.S. licensed vaccines from health care providers, manufacturers, and the public. The FDA continually monitors VAERS reports for any unexpected patterns or changes in rates of adverse events.

35. Mention two drug products recalled with associated adverse events

Innoveix Pharmaceuticals, Inc.	Injectable Semorelin / Ipamorelin 3mg and injectable AOD-9604 3mg	Potential lack of sterility assurance

A drug recall is the most effective way to protect the public from a defective or potentially harmful product.

Teva	Topotecan Injection 4 mg/4 mL (1 mg/mL)	Presence of pavb rticulate matter

36. What are case reports and give its significant

A **case report** is a detailed **report** of the diagnosis, treatment, response to treatment, and follow-up after treatment of an individual patient.

The major advantage of case reporting is probably its ability to detect novelties . It is the only way to present unusual, uncontrolled observations regarding symptoms, clinical findings, course of illness, complications of interventions, associations of diseases, side effects of drugs, etc.

37. List out the purpose of meta analysis

A **meta-analysis** is a statistical analysis that combines the results of multiple scientific studies.. **Meta-analyses** are conducted to assess the strength of evidence present on a disease and treatment. One **aim** is to determine whether an effect exists; another **aim** is to determine whether the effect is positive or negative and, ideally, to obtain a single **summary** estimate of the effect.

38. Explain the potential contributions of PEY studies.

The potential contributions of pharmacoepidemiology include:

(1) supplemental information to premarketing studies and better quantifying the incidence of known adverse and beneficial effects in certain populations not studied prior to marketing (e.g., elderly, children, or pregnant women),

(2) new types of information not available from premarketing studies (e.g., undetected adverse and beneficial effects, patterns of utilization), and

(3) reassurances about drug safety and fulfillment of ethical and legal obligations.

In summary, questions that pharmacoepidemiologic studies can answer include:
(1) How and why is drug therapy being used/misused or prescribed?
(2) What are the beneficial and harmful outcomes of drug therapy?
(3) What interventions are effective in modifying the use and outcomes of drug therapy?

39. Define Ad-Hoc studies and enumerate the strength of Ad-Hoc studies?

Ad hoc is a Latin phrase meaning "for this". It generally signifies a solution designed for a specific problem or task.

Common examples are organizations, committees, and commissions created at the national or international level for a specific task.

The data sources available for pharmacoepidemiological studies as Ad hoc sources are those that are collected during post marketing surveillance studies

Ad hoc is concerned mainly with one specific purpose i.e providing data regarding drug safety in long term use or about the drug aspects in a large population which is seen in post marketing studies compared to pre marketing studies.

advantages-

- ☐ 1. not influenced by prior knowledge & investigators bias

2. It is objective, transparent and reproducible

40. Explain the need of pharmacoeconomics.
Pharmacoeconomics is needed for the following reasons:
1. Rising health expenditures have led to the necessity to find the optimal therapy at the lowest price. Pharmacoeconomics is an innovative method that aims to decrease health expenditures, whilst optimising healthcare results.
2. Pharmaceutical expenditures, which constitute a large part of healthcare expenditures, have been increasing much faster than total healthcare expenditures.
3. Numerous drug alternatives and empowered consumers also fuel the need for economic evaluations of pharmaceutical products.
4. The increasing cost of healthcare products and services has become a great concern for patients, healthcare professionals, insurers, politicians and the public. 5. This increasing concern has prompted demand for the use of economic evaluations of alternative healthcare outcomes.

41. Write two applications of CMA.
APPLICATION OF CMA
- ♦ In situations where the benefits of alternative treatments have been proven to be identical and as such this methodology is perceived as being easy to apply.
- ♦ It is used in supporting and justifying the introduction of cheaper drugs in the same therapeutic class.
- ♦ It is used when finding out the activity or output with the lowest cost

42. Enlist types of errors
    a. random error
    b. systematic error

TYPES OF ERROR:

♦ Random error/Non-differential: use of invalid outcome measure that equally misclassifies cases and controls

♦ Systematic error/Differential: use of an invalid measure that misclassifies cases in one direction and misclassifies controls in another

43. Define DUE

    Drug utilization evaluation is defined as an authorized, structured, ongoing review of prescribing, dispensing and use of medication. DUE encompasses a drug review against predetermined criteria that results in changes to drug therapy when these criteria are not met. It involves a comprehensive review of patients' prescription and medication data before, during and after dispensing to ensure appropriate medication decision-making and positive patient outcomes.

44. Define risk in PEY.

    Risk is not certain. • Risk is based on probability. Therefore, not everyone who is exposed to a risk condition or factor will have an adverse outcome. Risk factors are "linked to" and "associated with" negative outcomes. • E.g. psychosocial outcomes v/s biological outcomes • Teratogenic drug – thalidomide, environmental toxin – lead

    Risk is a relative concept. • Risk factors range from those that are only markers to minimally harmful situations to those that are markers to life – threatening situations. • (Social continuum of risk/personal risk continuum)

45. Define vaccine safety.

Vaccine safety

The process of ensuring and monitoring the safety of vaccines through their life cycle.

Passive **surveillance** is defined as unsolicited reports of adverse events that are sent to a central database or health authority. In the United States, these are received and entered into the **Vaccine** Adverse Event Reporting System (VAERS) that is co-managed by FDA and CDC.

46. Role of pharmacist in essential drug concept.
    1. Member of Drug and Therapeutic Committee. 2. Drug procurement. 3. Drug storage. 4. Dispensing. 5. Patient education. 6. Drug information service. 7. Pharmaceutical care.

47. Write the objectives of pharmacoepidemiology.

    The three objectives of pharmacoepidemiology became clear: to study the effectiveness, safety and utilization of drugs in the real-world of practice.

48. What are the strengths and weakness of Medicaid and Medicare.

Advantages of Medicaid

1. Medicaid is a program that focuses on both elderly individuals and individuals who suffer from various disabilities. More specifically, seniors and disabled individuals have been shown to account for approximately two-thirds of medical aid spending in the United States.
2. Those who are on Medicaid will find that their patient copay costs are generally lower and much more affordable.

Disadvantages of Medicaid

1. While Medicaid is, as previously mentioned, designed to serve lower-income individuals, not all low-income individuals will actually qualify for this service. Each state has its own set of specific guidelines in terms of qualifying for Medicaid.
2. In the event that someone on Medicaid ends up suffering an emergency, they can sometimes end up enduring lower quality treatment simply because they are on Medicaid. On Medicaid, the affected individual may not be able to undergo some of the necessary treatment.

Medicare is wonderful. Medicare's fee structure, low co-pay, easy administration, wide acceptance, broad coverage and low restrictions make it most useful

Patients and medical professionals can and do abuse the system. LIMITED CLINICAL information. It does not have pharmacy benefit for outpatient medications thus the benefits cannot be studied.

76. Write two applications of Cost of illness analysis.

a. study of QOL

B. Cost-of-illness analysis represents another measure of disease burden that incorporates costs of disease.

78. Define cost utility analysis.

Cost-utility analysis (CUA) is a method for comparing treatment alternatives that integrates patient preferences and Health Regulated Quality of Life (HRQOL) . HRQOL measure is an utility, having value between 1.0 (perfect health) and 0.0 (death). Quality-adjusted life years (QALYs) are then derived by multiplying the time in a health state by the appropriate utility score. In CUA, Cost is measured in dollars, and therapeutic outcome is measured in patient-weighted utilities rather than in physical units

81. Define hospital pharmacoepidemiology.

IT is a study which basically analyses the situation and gap assessment in the hospital regarding reporting of ADRs, data management and also planning of operational research in the hospital.

82. Write a note on rational use of drugs.

rational use means "prescribing right drug, in adequate dose for the sufficient duration & appropriate to the clinical needs of the patient at lowest cost

WHO: The rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, and at the lowest cost to them and their community

33. Write the advantages of PEY studies.

Pharmacoepidemiological studies have the potential to provide much needed insight into treatment effects and risk factors for adverse effects once a drug is used in a larger and more diverse population than the clinical trial programme would enrol

34. What are the strengths and weakness of computerised database.

Advantages

- Reduced data redundancy
- Reduced updating errors and increased consistency
- Greater data integrity and independence from applications programs
- Improved data access to users through use of host and query languages
- Improved data security
- Reduced data entry, storage, and retrieval costs
- Facilitated development of new applications program

Disadvantages

- Database systems are complex, difficult, and time-consuming to design
- Substantial hardware and software start-up costs
- Damage to database affects virtually all applications programs
- Extensive conversion costs in moving form a file-based system to a database system
- Initial training required for all programmers and users

35. Write the aims of pharmacoeconomic studies.

Pharmacoeconomics research identifies measures and compares the costs and outcomes of pharmaceutical products and services. Pharmacoeconomics can play a significant role in the efficient allocation of resources in healthcare systems with constrained budgets.

It runs through the thread of our socioeconomic system, which regulates and influences all the sectors involved in pharmaceuticals. The demand for and the cost of health care are increasing in all countries as the improvement of health technologies. All over the world, patients are affected by high price of medicines. In a developing country like India, 85% of total health expenditure is financed by house-hold out of pocket expenditure. Many poor people frequently face a choice between buying medicines or buying food or other necessities due to limited resources and high pricing of drug

36. Write the applications of cost utility analysis.

Well-known application of cost utility analysis is in the health sector, with the use of Quality Adjusted Life Years (QALYs). The QALY allows each potential program to be measured according to the extent to which it extends life expectancy while also improving the quality of each year lived

Length of life (quantity) and quality of life are different

¬ Length of life (quantity) is unaffected and quality of life is different

¬ Outcomes are very different

¬ CUA is not warranted when: Number of life years saved (quantity) is different but quality of each year of life is very similar

When to use CUA?
¬When health related quality of life is important outcome. • E.g. Treatment of arthritis may have no impact on mortality, but interest is focused on how well the different interventions improves patient's physical function, social function and psychological well- being. • Cancer: Treatment of cancer may extend life but at the expense of side effects

¬When intervention affects both morbidity and mortality and a common unit of outcome is desired
¬When a program being compared have a wide range of different kinds of outcomes and a common unit of outcome is desired for comparison ♣ Provision of ARVs vs. Polio Vaccination ♣ Malaria program vs TB program

37. What is the significance of post marketing surveillance?

insights they gain through post-market surveillance activities to:

- Detect adverse events or risks as they arise during real-world usage of a device or drug.
- Compare new products or treatments with existing options and the standard of care.
- Update clinical guidelines as certain populations or groups find more benefit than others.
- Comply with regulatory requirements.

38. Define direct costs.

Direct Medical Costs: Costs of medical service These include: • Fixed costs or costs that do not vary immediately with the number of patients treated. E.g. capital costs of hospital building or equipment etc. • Variable costs or costs that vary immediately with number of patients treated. E.g. costs of drugs, syringes, needles etc.

90. Enumerate the difference between relative risk and attributable risk

Relative Risk vs. Attributable Risk

Relative Risk: Measure of the strength of association, and indicator used to assess the possibility of a causal relationship.

Attributable Risk: Measure of the potential for prevention of disease if the exposure could be eliminated (assuming a causal relationship).

91. Enlist two birth defects.

a. fetal ototoxicity have been described after maternal exposure to either streptomycin or its congener dihydrostreptomycin

b. Cidofovir : complications - Possible external, soft tissue, and skeletal anomalies (ie, meningocele, short snout, short maxillary bones) of the fetus.

c. Fluconazole: Associated defects and complications - Craniofacial, skeletal, and cardiac effects

92. **What do you mean by essential drug list**

Essential drug list, as defined by the World Health Organization (WHO), are the **medicines** that "satisfy the priority health care needs of the population". These are the **medications** to which people **should** have access at all times in sufficient amounts. The prices **should** be at generally affordable levels.

LONG ESSAYS 10 MARKS

1. **Define risk & enlist the various factors influencing risk in pharmacoepidemiology. Explain relative risk and Odd's ratio with suitable examples.**

- **RISK:** Risk is that the likelihood (or) the probability of experiencing some sort of harm (or) losing something that one values.

- Risk factors are variables or characteristics (biological - genetic disorder/ageing, environmental- air/water pollution/ passive smokingor psychosocial- workload/deadlines) associated with an individual that make it more likely that he or she, as opposed to another person randomly selected from the population, will develop a problem.

- RISK FACTORS:
    1. Exists before a disorder or problem;
    2. Maybe time – limited or may continue over time;
    3. Can derive from the individual, the family, the community, institutions or the general environment; and
    4. Can play a causal role or be a marker for a problem (BRAC).

CHARACTERISTICS OF RISK:

1. Risk isn't certain.

Risk is predicated on probability. Therefore, not everyone who is exposed to a risk condition (or) factor will have adverse outcome.

2. Risk may be a relative concept.

Risk factors range from people who are only markers to minimally harmful situations to people who are markers of life-threatening situations.

Risk factors work together overtime to influence the likelihood of a negative outcome.

The longer the exposure to risk factors, the greater the likelihood the ill health will occur.

RISK IN PHARMACOEPIDEMIOLOGY:

- Health research involves the estimation of risk.
- In the case of drug related research, it's important to know the concept of risk.
- It is that the probability of developing an outcome when exposed to a drug.
- A drug is approved for human use only after measuring the risks and benefits related to it.
- Pharmacists should know the magnitude and frequency of the danger involved within the drug in use.
- Each drug outcome has its own risk.
- It may be a probability and depends on a spread of things like age, sex, physical conditions, food habits, other diseases, other medicines, kinetics of medicine etc.

RELATIVE RISK

- Relative risk is additionally called us risk ratio.
- It is that the ratio of the probability of an occasion occurring (Ex: development of an adverse drug reaction to a drug) in an exposed group to the probability of the event occurring in non-exposed group.
- RR above 1 indicates treatment or exposure is related to the result and below 1, means the treatment is negatively related to the result .
- When the speed within the exposed group is adequate to the speed within the comparison group RR are going to be adequate to 1.
- An RR of two means, the speed within the exposed group is twice that of non exposed group.
- An RR of 0.5 means, the speed within the exposed persons is half that of non exposed persons.

The table below shows how the risk ratio was calculated in the study examining the risk of wound infections when an incidental appendectomy was done during a staging laparotomy for Hodgkin disease.

Had Incidental Appendectomy?	Wound Infection	No Wound Infection	Total	Cumulative Incidence
Yes	7	124	131	7/131 = 5.34%
No	1	78	79	1/79 = 1.27%

Risk Ratio = 5.34/1.27 = 4.2

ODDS RATIO

- It may be a measure of association between an exposure and an outcome like "relative risk".
- Odds ratio in statistics and Epidemiology is usually abbreviated as "OR".
- Like "relative risk" determines probabilities, in OR odds are used.

How to find Odds?

Ex: You have two choices for the formula:

(a/c) / (b/d)

or, equivalently:

(a*d) / (b*c)

Interpretation:

• OR of 1 would suggest that there's no difference between the groups, i.e., there would be no association between the suggested exposure and outcome being ill.

• OR of >1 suggests that the chances of exposure are positively related to an adverse outcome compared to the chances of not being exposed.

• OR of <1 suggests that the chances of exposure are negatively related to an adverse outcome compared to the chances of not being exposed.

2.What is bias. Explain the different types of bias in pharmacoepidemiology with examples.

Bias is a systematic error in sampling or measurement that leads to an incorrect conclusion.

Types of Bias

Several types (e.g. referral, recall, differential, non-differential, etc.) It is usually subdivided into 1) Selection Bias: Related to study subject recruitment or retention procedures

2) Information Bias: Related to procedures used to measure the information about study variables

3) Confounding: Distortion caused by other variables to both exposure & outcome

The risk of Protopathic Bias (Reverse Causality) is believed to occur only in PE studies.

Selection Bias

• Bias of the estimated effect of an exposure on an outcome due to conditioning on a common effect of the exposure and the outcome (or of causes of the exposure and the outcome)

• Distortions that result from procedures used to select subjects and from factors that influence participation in the study. A distortion in the estimate of the effect due to the manner in which subjects are selected for the study.

Selection Bias - Examples

• Subject selection is influenced by

Exposure → Case-Control

Q) Are cases & controls selected from the same population?

- Hospital based recruitment to study NSAIDs & abdominal pain

Risk of AE → Cohort

Q) Does recruitment of exposed and non-exposed relate to their likely development of the outcome of interest?

-A recent publication may condition and increase the probability of diagnostic testing of "interesting cases". • Includes Referral, Self-Selection and Prevalence Bias.

Information Bias - Definition • A flaw in measuring exposure, covariate or outcome variables that results in different quality (accuracy) of information between comparison groups. It may not be independent of the occurrence of selection bias.

Information Bias - Examples

• Non-differential (random) misclassification → may affect statistical significance
- Commonly mentioned as limitation of PE studies
- Somehow difficult to control (… the "unknowns")
- e.g. Non-validated diagnostic criteria (medical services DB); Exposure ascertainment (prescription vs. actual drug use; choice of time point vs. previous exposure history)

10% Non-differential misclassification of Exposures

	AE +	AE -
Exp+	20	10
Exp-	80	90

	AE +	AE -
Exp+	20 ↓2	10 ↓1
Exp-	80 ↑8	90 ↑9

	AE +	AE -
Exp+	26	18
Exp-	74	82

True OR = 2.25
(20x90)/(80x10)

Estimated OR = 1.60
(26x82)/(74x18)

Bias towards null

Information Bias - Examples

• Non-differential (random) misclassification → may affect statistical significance
- Commonly mentioned as limitation of PE studies
- Somehow difficult to control (… the "unknowns")
- e.g. Non-validated diagnostic criteria (medical services DB); Exposure ascertainment (prescription vs. actual drug use; choice of time point vs. previous exposure history)

10% Non-differential misclassification of Exposures

	AE +	AE -
Exp+	20	10
Exp-	80	90

	AE +	AE -
Exp+	20 ↓2	10 ↓1
Exp-	80 ↑8	90 ↑9

	AE +	AE -
Exp+	26	18
Exp-	74	82

True OR = 2.25
(20x90)/(80x10)

Estimated OR = 1.60
(26x82)/(74x18)

Bias towards null

Confounding - Definition

• Distortion of a measure of the effect of an exposure (Drug use) on an outcome (Adverse Event) due to the association of the exposure with other factors (Confounders) that influence the occurrence of the outcome

Protopathic Bias

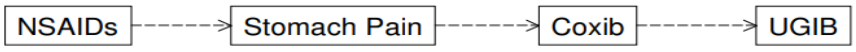
Definition

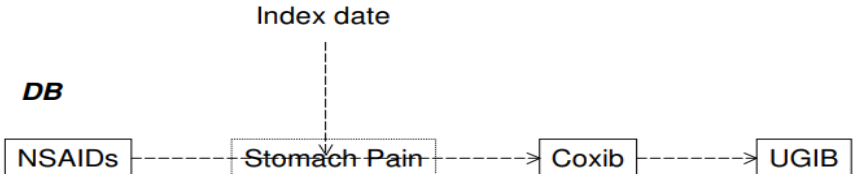
A type of bias that occur if the first symptoms of the outcome of interest are the reasons for using the treatment under study (i.e. to become exposed).

If there is a delay between the first symptoms of an AE (for Drug A) and the diagnosis

The AE (for Drug A) may be incorrectly associated to the Drug B, which was prescribed to replace it (or to treat the symptoms)

Truth





3. **What is medication adherence. Explain the methods used to assess medication adherence.**
   - The WHO defines *adherence* as "the extent to which the persons' behavior (including medication-taking) corresponds with agreed recommendations from a healthcare provider". It includes the *initiation* of the treatment, *implementation* of the prescribed regime, and *discontinuation* of the pharmacotherapy.
   - classification of adherence measures as *direct* and *indirect* .
   - Direct measures include measurement of the drug or its metabolite concentration in body fluids, such as blood or urine and evaluation of the presence of a biological marker given with the drug and direct observation of patient's medication-taking behavior. These measures can be made randomly or at specific intervals.

Measures Involving Secondary Database Analysis

Medication Possession Ratio (MPR)

- Andrade et al. defined MPR as the proportion (or percentage) of days' supply obtained over either *refill interval*, where last refill is the end point, or *fixed* refill, where a specific time period is

set . The former is used in the case such as patients with depression or HIV whereas the latter is generally used for assessing seasonal use of medication, asthma or allergies, and so forth.

Dichotomous Variable

- This measure requires a cutoff value to distinguish adherence and nonadherence or adherence from partial adherence. Compared to the continuous variable, it has lower sensitivity probably due to its general lack of pharmacological basis for deciding the cutoff value.

Continuous, Multiple Interval Measure of Medication Acquisition (CMA)

- CMA is calculated as the cumulative days' supply obtained over a series of intervals divided by the total days from the beginning to the end of the time period in study. The overall average of all participants' CMA provides the adherence value of the entire time period of the study.

Measures Involving Electronic Medication Packaging (EMP) Devices

EMP devices are "adherence-monitoring devices incorporated into the packaging of a prescription medication." With several choices available, they share some common features: (i) recorded dosing events and stored records of adherence; (ii) audiovisual reminders to signal time for the next dose; (iii) digital displays; (iv) real-time monitoring; and (v) feedback on adherence performance

---

Pill Count

This indirect, objective measure counts the number of dosage units that have been taken between two scheduled appointments or clinic visits. This number would then be compared with the total number of units received by the patient to calculate the adherence ratio

---

Measures Involving Clinician Assessments and Self-Report

Many authors believe that these subjective methods are the least reliable among all. Nevertheless, their low cost, simplicity, and real-time feedback have contributed to their popularity in clinical practice. They can be administered as structured interviews, online assessments, written questionnaires, voice response system, and so forth. Additionally, due to their practicality and flexibility, these questionnaires are able to identify individual patient concerns and subsequently tailor appropriate intervention

OR

Medical adherence measurements

I. Biological Assays
II. Pill counts
III. Weight of topical medications
IV. Electronic monitoring
V. Patient interviews

I. Biological Assays

- Biological assays measure the concentration of a drug, its metabolites, or tracer compounds within the blood or urine of a patient.
- These measures are intrusive and sometimes costly to administer.
- Drug or food interactions, physiological differences, dosing schedules, and therefore the half-life of the drugs may influence the results.
- Biological tracers that have known half lives and don't interfere with the medication could also be used, but there are ethical concerns.
- All of those methods have high costs for the assays that limit the feasibility of those techniques.

II. Pill Counts

- Counting the amount of pills remaining during a patient's supply and calculating the amount of pills that the patient has taken since filling the prescription is that the simplest way for calculating patient medication adherence.
- Patterns of non-adherence are often difficult to discern with an easy count of pills on a particular date weeks to months after the prescription was filled.
- Because pill counts are often based upon the date a prescription is filled, patients who get prescriptions refilled before their first one may present complications.

III. Weight of Topical Medications

- The weight of a topical medication remaining during a tube is employed as a measure of adherence.
- When compared with patient log books of daily medication use, weight estimates of adherence were considerably less than patient log estimates.
- In a comparison of methods to live adherence, found that estimates calculated from medication logs and drugs weights were consistently above those of electronic monitors.

IV. Electronic Monitoring

- The Medication Event Monitoring System (MEMS) manufactured by Aardex Corporation allows the assessment of the amount of pills missed during a period also as adherence to a dosing schedule.
- The system electronically monitors when the bottle is opened, and therefore the researcher can periodically download the knowledge to a computer.
- The availability and price of this technique could limit the feasibility of its use.

v. Patient interviews

- Interviewing the patients to assess their knowledge of the medications they need been prescribed and therefore the dosing schedule provide information on whether the patient is adherent with the particular dosing schedule.

4. **Identify and explain the two major pharmacoepidemiological models used to test the relationship between drug exposure and patient outcomes.**
   (ans: cohort and case controlled studies
   Measure cohort via relative risk and case controlled via odds ratio)

5. **Explain the applications of pharmacoeconomics.**

APPLICATION OF PHARMACOECONOMICS

Pharmacoeconomics is useful in taking the subsequent activities:

1. Formulary Decision Making:

Drug is compared with the available alternative(s) with reference to safety, cost and efficacy/effectiveness.
Pharmacoeconomic evidence of superiority for brand spanking new treatments at the time of drug registration is mandatory in some countries.
Literature are often the source for formulary decision supported studies.

2. Treatment Guidelines:

Establishing guidelines starts from the evaluation of the available treatments and their efficacy and safety.
Evaluation occurs when the new treatment demonstrates a far better efficacy and safety profile but also a better cost.

3. Individual Patient Treatment Decision:

Pharmacoeconomic studies may guide clinicians in making CEA choices for specific categories of patients.
Pharmacoeconomic studies are designed to guage the prices and benefits for a population of patients responding to a group of general characteristics.
Patient specific factors like drug allergies, therapeutic failure or lack of coverage can make a price effective agent a poor choice for a private patient.

4. Others:

(a) Research services
Customized PE studies.
Site or population.
Specific economic models.
(b) Educational services
PE lectures and workshops.
PE educational materials.
(c) Consulting services
Protocol design and strategic PE plans.

6. **Define DUE. Explain the steps involved in a DUE and mention the pharmacist role in DUE cycle.**

According to WHO, Drug Utilization evaluation is defined as the marketing, distribution, prescription and use of drugs in society, with special emphasis on the resulting medical, social and economic consequences. Drug Utilization Evaluation (DUE) is an ongoing authorized and systematic quality improvement process, designed to:

- To optimize drug use by developing criteria and standards.
- To educate clinicians and other Health Care Professionals (HCP), to increase appropriate drug use.
- To provide feedback of results obtained during study to clinicians and other HCP.
- To review drug use.
- To analyze prescription pattern.

DUE cycle

It is important to keep in mind that DUE operates in a repeating cycle.
The DUE cycle should include the following seven major activities or phases:
1.Planning (step 1-4)

2.Data collection (step 5)
3.Evaluation (step 6)
4.Feedback if results (step 7)
5.Interventions (step 8)
3.Re-evaluation (step 9-10)
7.Feedback of results (step 11)

STEPS INVOLVED IN CONDUCTING A DUE CYCLE

Step 1: Identify drugs or therapeutic areas of practice for possible inclusion in the program.

•The DUE committee must identify priority drugs or areas of practice where improvement in use will result in the greatest clinical impact.
•These areas can be identified through various sources of information such as medication error reports, ADR reports, feedback from prescribers or clinical pharmacists, local microbiological data and medical and pharmaceutical literatures
•ABC or VEN analysis is another important tool used to identify high priority or target drugs.
•ABC analysis divides the drugs into three classes based on their annual usage:
a) Class A drugs constitute 75-80% of the total values of drugs consumed or purchased and are the highest cost or highest volume items.
b) Class B items constitute 15-20% of expenditure.
c) Class C includes low cost or low volume items, which form 5-10% of expenditures.
•ABC analysis is generally done to assist the selection of drugs to be included in the hospital formulary.
•In VEN analysis the drugs are generally classified as vital (V), essential (E) and non- essential (N)
•Common targets for DUE include:
a) Drugs with a narrow therapeutic index such as digoxin, phenytoin, cyclosporine, theophylline, etc.
b) Drugs used in the management of common conditions such as chronic pain, respiratory tract infections or urinary tract infections
c) New drugs
d) Commonly prescribed drugs such as antibiotics and PPIs
e) Expensive drugs such as low molecular weight heparin, broad-spectrum cephalosporin, anti-HIV medications.

Step 2: Design of study.

Research methods:
1.Observational research method: most commonly used.
2.Experimental methods: E.g. Randomized controlled trials.
3.Cross-sectional studies: Drug use is examined at a single point in time, are useful for problem identification.
Based on design of study, DUE studies may also be categorized as prospective, concurrent, retrospective depending on the timing of data collection.

Step 3: Define criteria and standards.

•After the DUE target has been selected, it is important to conduct a comprehensive literature review.
•The step involved in literature review are:
1.Perform an exhaustive literature search for the chosen drug or therapeutic area using multiple search mechanisms such as medical (Medline, Micromedex, Drugdex, Cochrane library, Embase) and pharmacy based systems (IOWA, drug information service, international pharmaceutical abstracts).
2.Assemble full copies (not just the abstracts) of all the relevant original research papers.
3.Critically evaluate the studies directly relevant to the chosen drug or therapeutic area. This includes identifying strengths and weakness in the study design and deciding whether appropriate conclusions have been made from the data prescribed.

4.Briefly summarize the literature review, identifying the key papers in the chosen area and the drug use criteria that can be derived from the evidence- based literature.

Step 4: Design the data collection form.

As it is impossible to monitor and evaluate all the drugs used in a hospital, it is also impossible to address all aspects of use for each drug.

It is important to limit data collection to only the most important and relevant aspects of drug use and to factors which may influence these.

Some aspects of drug use which are commonly surveyed during DUE are:

1. Patient demographics
2. Prescriber details
3. Disease severity
4. Co-morbidities
5. Indication for drug use
6. Drug-disease contraindications
7. Side or adverse effects
8. Dosing information
9. Duration of drug treatment
10. Drug or drug class duplication
11. Therapeutic duplication
12. Preparation and administration
13. Drug-drug and drug-food interactions
14. Monitoring of drug therapy
15. Patient education or instructions
16. Cost of therapy
17. Over or under utilization of drugs

Step 5: Data collection.

- Data collectors should be chosen carefully and should be familiar with how information is arranged in the patients case notes.
- Knowledge of drug names, strength and the way orders are written is also important.
- Depending on their availability, physicians, pharmacists and nurses make ideal data collectors.

Step 6: Evaluate results.

- Data evaluation is one of the most critical steps in a DUE.
- The data obtained should be collected using available resources such as spread sheeting, data basing and word processing.
- The next step is to summarize the main categories of results and to identify where exactly the data shows deviation should be evaluated.

Reasons for deviation may include:

1. Drug being used for new indications.
2. Outdated procedures.
3. Inadequate resources.
4. Gaps in knowledge or misinformation or misunderstanding.

Step 7: Provide feedback of results.

The success of any DUE strategy depends on feedback of the results to prescribes, other hospital staff involved in the study and to administrative heads.

- The presentation of any report is also very important.
- The report should be well-presented and well-reasoned document with no grammatical or typographical errors.

•It is important to prepare a scientific interpretation of the results rather than a value judgment.
•The results can also be circulated to hospital staff through newsletters. DUE meetings or the hospitals academic meetings.

Step 8: Develop and implement interventions.

- If a drug use problem was identified, the next step is to consider how the problem can be addressed.
- Interventions to improve drug use can be educational meetings, academic detailing, circulation of protocols, feedback of study results, letters to individual physicians, newsletters and other informational materials such as posters and guidelines.

•Operational interventions include the development or modification of drug other firms manual or computerized reminders, prescribing restrictions, formulary additions or deletions, automatic stop orders or reallocation of staff.
•The choice and development of interventions require careful planning.

Step 9: Re-evaluate to determine if drug use has improved.

- Drug use and prescribing patterns need to be monitored to determine the success of interventions.
- Re-evaluation is done 3-12 months after the introduction of intervention, and should involve collecting the same data as in the original DUE evaluation.

Step 10: Re-access and revise the DUE program.

At the end of an evaluation cycle, the DUR Committee should perform an evaluation of the DUR program, and if necessary, make policy and procedural changes to reflect actual practices, or to facilitate desired changes. Other considerations when evaluating the program are:

1. Were appropriate drugs chosen for inclusion?
2. Did the program address important aspects of care?
3. Were criteria developed according to hospital policy?
4. Were thresholds appropriate?
5. Were problems identified?
6. Were interventions appropriate?
7. Was drug use problems solved/did drug therapy improved?
8. Did DUR have an impact on the incidence of adverse drug reactions, drug- drug interactions, or medication administration errors (if there is a system already in place for monitoring them)?
9. Were results disseminated according to policy?
10. Did the DUR program have a financial impact on the hospital?

Step 11: Feedback of results.

1. It is important to circulate the results of the DUE to clinicians and other involved hospital staff.
2. This is also a suitable time to obtain their opinions about the success or otherwise of the interventions and how these can be improved.

ROLE OF PHARMACIST IN DUE:

- Planning, organizing and implementing a DUE program.
- Program, development, supervision and coordination.
- Education of hospital staff about DUE in conceptual an practical terms.
- Promotion of the goals and objectives of DUE.
- Development or review of audit criteria, guidelines, study protocols and educational materials.
- Development of data collection, analysis and report writing
- Documentation of program outcome, effectiveness and cost benefits.
- Participation in hospital committees concerned with quality assurance in general and drug usage.
- Presentation of DUE results at meeting and conferences.

- Publication of results in peer-viewed journals.

7. Explain the merits and demerits of Cohort and case controlled study.

17. Explain in detail the cohort studies in Pharmacoepidemological study designs and explain in detail the cohort classification?

COHORT STUDY:

a cohort study may be a study of groups of patients having some common drug exposure of interest.

Examples of Cohort include:

- Pharm.D students of particular college of pharmacy.
- Patients coming to a specific hospital.
- People with a specific genetic trait or adults admitted during a specialty hospital.

In a cohort study, a gaggle of people exposed to a putative risk factor and a gaggle who arc unexposed to the danger factor are followed over time (often years) to work out the occurrence of disease.

The incidence of disease within the exposed group is compared with the incidence of disease within the unexposed group.

The relative risk (incidence risk or incidence rate) is employed to assess whether the exposure and disease are causally linked.

Cohort studies are often prospective or retrospective in nature.

Prospective Cohort Study:

- A prospective cohort study is additionally called a concurrent cohort study, where the themes are followed up for a period and therefore the outcomes of interest are recorded.
- It is taken into account because the best sort of cohort study as far as scientific evidence and control over the factors of interest are considered. it's forward in time and allows the researcher maximum control over the study definition and its conduct. The potential confounding factors and variables that has got to be controlled within the study process are often defined and measured in prospective cohort studies. it's very expensive.

Retrospective Cohort Study:

- The retrospective cohort study looks back on existing data. Generally the info come from medical records and electronic database . While this sort of cohort study is a smaller amount time consuming and dear than a prospective cohort study, it's more vulnerable to the consequences of bias. for instance , the exposure may have occurred some years previously and adequate reliable data on exposure could also be unavailable or incomplete.
- In addition, information on confounding variables could also be unavailable, inadequate or difficult to gather .

Issues within the design of cohort studies:

Selection of study groups:

- The aim of a cohort study is to pick study participants who are identical with the exception of their exposure status. All study participants must be freed from the result under investigation and have the potential to develop the result under investigation.

Measuring exposure:

• Levels of exposure (e.g. packs of cigarettes smoked per year) are measured for every individual at baseline at the start of the study and assessed at intervals during the amount of follow-up. When several exposures are being considered simultaneously, the non-exposed group should comprise all those with none of the danger factors under investigation.
• A particular problem occurring in cohort studies is whether or not individuals within the control group are truly unexposed. for instance , study participants may start smoking or they'll fail to properly recall past exposure. Similarly, those within the exposed group may change their behavior in reference to the exposure like diet, smoking or alcohol consumption.
• Exposure data could also be obtained from variety of sources including medical or employment records, standardized questionnaires, interviews and by physical examination.

Measuring outcome:
• Outcome measures could also be obtained from various sources, including routine surveillance of cancer registry data, death certificates, and medical records or directly from the participant. Note that the tactic wont to ascertain outcome must be identical for both exposed and unexposed groups.

Methods of follow-up:
• The follow-up of study participants during a cohort study may be a major challenge. an excellent deal of cost and time is required to make sure follow-up of cohort members and to update measures of exposures and confounders, additionally to monitoring participant's health outcomes. The failure to gather outcome data for all members of the cohort will affect the validity of study results.

Potential sources of bias in cohort studies:
• A major source of potential bias in cohort studies is thanks to losses to follow-up. Cohort members may die, migrate, change jobs or refuse to still participate within the study. additionally , losses to follow-up could also be associated with the exposure, outcome or both. for instance , individuals who develop the result could also be less likely to still participate within the study. The degree to which losses to follow-up are correlated with exposure and outcome will cause serious bias within the measures of effect of exposure and outcome.
• A major source of potential bias in cohort studies arises from the degree of accuracy with which subjects are classified with reference to their exposure or disease status. Differential misclassification can cause an over or underestimate of the effect between exposure and outcome.

Selection bias in cohort studies:
• Selection bias may be a potential problem in case-control studies. Selection bias could also be introduced when the completeness of follow-up or case ascertainment differs between exposure categories. this will be minimized by ensuring that a high level of follow-up is maintained among all study groups.

The healthy worker effect:
• The healthy worker effect is another potential sort of selection bias in cohort studies, particularly affecting occupational studies. In an occupational cohort study where disease rates among individuals from a specific vocation are compared with an external standard population, bias could also be introduced if membership of the exposed cohort is partly dependent upon health (which could also be associated with the presence or absence of the health outcome under investigation).
• Individuals, who are employed, for instance , are generally healthy naturally of their ability to figure Therefore, mortality or morbidity rates within the occupation group cohort could also be initially less than within the population as an entire , which incorporates individuals who are too ill to figure
• In order to attenuate the potential for this type of bias, a comparison group could also be selected from a gaggle of workers with different jobs performed at different locations within one facility. for instance , a gaggle of non-exposed office workers. Alternatively, the comparison group may he selected from an external population of employed individuals.

Analysis of cohort studies:

• Analysis of a cohort study uses either the danger or the speed ratio of disease within the exposed cohort compared with the speed or risk within the unexposed cohort.

• Note that the danger ratio uses as a denominator the whole group recruited at the beginning of the study, while the speed ratio uses as a denominator the person years, which takes account of losses to follow-up.

ADVANTAGES and drawbacks OF COHORT STUDIES

Advantages:

• Subjects in cohorts are often matched, which limits the influence of confounding variables.

• Standardization of criteria/outcome is feasible .

• Easier and cheaper than a randomized controlled trial (RCT).

Disadvantages:

• Cohorts are often difficult to spot thanks to confounding variables.

• No randomization, which suggests that imbalances in patient characteristics could exist.

• Blinding/masking is difficult.

• Outcome of interest could take time to occur.

CASE CONTROLLED STUDY

A case-control study is meant to assist determine if an exposure is related to an outcome (i.e., disease or condition of interest). In theory, the case-control study are often described simply, First, identify the cases (a group known to possess the outcome) and therefore the controls (A group known to be freed from the outcome).

• Then, reminisce in time to find out which subjects in each group had the exposure(s), comparing the frequency of the exposure within the case group to the control group. By definition, a case-control study is usually retrospective because it starts with an outcome then traces back to research exposures.

• When the themes are enrolled in their respective groups, the result of every subject is already known by the investigator. This, and not the very fact that the investigator usually makes use of previously collected data, is what make case-control studies 'retrospective'.

Cases

• Consider a situation during which an outsized number of cases of post-operative endophthalmitis have occurred during a few weeks.

• The case group would contains all those patients at the hospital who developed post-operative endophthalmitis during a pre-defined period.

• The definition of a case must be very specific:

(1) Within what period of your time after operation will the event of endophthalmitis qualify as a case – at some point , one week, or one month?

(2) Will endophthalmitis need to be proven microbiologically, or will a clinical diagnosis be acceptable?

(3) Clinical criteria must be identified in great detail. If microbiologic facilities are available, how will patients who have negative cultures are classified?

(4) How will sterile inflammation be differentiated from endophthalmitis?

• There aren't necessarily any 'right 'answers to those questions but they need to be answered before the study begins. At the top of the study, the conclusions are going to be valid just for patients who have an equivalent kind of 'endophthalmitis' as within the case definition.

Controls

• Controls should be chosen who are similar in some ways to the cases.
• The factors (e.g., age, sex, time of hospitalization) chosen to define how controls are to be almost like the cases are the 'matching criteria'.
• The selected control group must be at similar risk of developing the outcome; it might not be appropriate to match group of controls who had traumatic corneal lacerations with cases who under-went elective intraocular surgery.
• In our example, controls might be defined as patients who underwent elective intraocular surgery during an equivalent period of your time .

Matching Cases and Controls

• Although controls must be just like the cases in some ways , it's possible to over-match. Over-matching can make it difficult to seek out enough controls. Also, once an identical variable has been selected, it's impossible to research it as a risk factor.
• Matching for sort of intraocular surgery (e.g., secondary IOL implantation) would mean including an equivalent percentage of controls as cases that had surgery to implant a secondary IOL; if this were done, it might not be possible to research secondary IOL implantation as a possible risk factor for endophthalmitis.
• An important technique for adding power to a study is to enroll quite one control for each case. For statistical reasons, however, there's little gained by including quite two controls per case.

Collecting Data

• After clearly defining cases and controls, choose data to be collected; an equivalent data must be collected within the same way from both groups.
• Care must be taken to be objective within the look for past risk factors, especially since the result is already known, or the study may suffer from researcher bias.
• Although it's going to not always be possible, it's important to undertake to mask the result from the one that is collecting risk factor information or inter-viewing patients.
• Sometimes it'll be necessary to interview patients about potential factors (such as history of smoking, diet, use of traditional eye medicines, etc.) in their past.
• It could also be difficult for a few people to recall of these details accurately. Furthermore, patients who have the out-come (cases) are likely to scrutinize the past, remembering details of negative exposures more clearly than controls. this is often referred to as recall bias. Anything the researcher can do to attenuate this sort of bias will strengthen the study.

ADVANTAGES & DISADVANTAGES OF CASE-CONTROL STUDIES

ADVANTAGES	DISADVANTAGES
• Can obtain findings quickly. • Can often be undertaken with minimal funding. • Efficient for rare diseases. • Can study multiple exposures. • Generally requires few study subjects.	• Cannot generate incidence data. • Subject to bias. • Difficult if records keeping are either inadequate or unreliable. • Selection of controls can be difficult.

8. Define pharmacoepidemiology and explain history and scope of pharmacoepidemiology.

Pharmacoepidemiology: The science concerned with the advantages & risk of medicine , utilized in populations & the analysis of the outcomes of drug therapies.

Origin of Pharmacoepidemiology & Evolution:

• In 1961, the case reports of maternal use of thalidomide, which produces malformations in offspring's, leads to awareness that, drugs cause ADR's.
• Since then, a greater attention was focused on the detection, prevention & management of ADR's & the age of pharmacoepidemiology have begun.
• The important ADR's detected through these systems include:
1. Grey baby syndrome thanks to CHLORAMPHENICOL.
2. Vaginal cancer in offspring's of girls , who took DIETHYL-STILBESTROL during pregnancy.
3. ISOTRETINOIN induces birth defects.
4. TRIAZOLAM induces CNS disturbances.
5. Suicidal ideation with FLUOXETINE.
6. Deaths with FENOTEROL. etc.
• In 1960, the related field of Drug Utilization (DU) was developed along side the study of ADR's.
• Previously DU studies were conducted mostly for marketing purposes & data weren't available to be used by health authorities.
• ISPE [International Society of Pharmacoepidemiology] was formed to get more data on risk & benefits of medicine in population & to debate , develop & disseminate information about Pharmacoepidemiology methods.

Need of Pharmacoepidemiology:

• Lack of other models to research some drug events.
Ex: to guage teratogenic effects of a replacement medicine.
• Clinical trials are inadequate to detect less common ADR's.
• Clinical trials conducted on highly selected patients with none co-morbidities and who taking no other medications.
• Clinical trials don't involve elderly, pediatric & pregnant patients.
• Clinical trials investigate the only indication.
Hence clinical trials fail to supply adequate information associated with safety & efficacy of a drug under non-trial conditions & in other indications.
In contrast, pharmacoepidemiology models provide alternative approaches to guage drug effects.

APPLICATION OF PHARMACOEPIDEMIOOLOGY:

1. Estimation of the risks of drug use:
• The risk involved in drug use are often estimated.
• Risks & benefits of use of a drug could also be weighed.
Ex: Case reports of Triazolam induced CNS disturbances appear soon after its introduction to plug .
The drug was withdrawn in some countries. The reaction was likely thanks to "Dose related". Hence the matter was solved by recommending a lower dose.
2. Use in patient counseling:
• Collection & analysis of observational data from other studies may help to deal with certain issues through counseling the patient.
Ex: A pregnant patient might need to terminate pregnancy, if there's a considerable risk for producing a seriously malformed child, but would also wish to proceed with the pregnancy, if the danger is low.
3. Formulation of public health policy decisions:
• Pharmacoepidemiology studies also help the policy makers to assess whether a drug should be withdrawn from the market or allowed to stay .
• Qualitative & quantitative information of PEY studies helps to deal with many issues.

EX: If an inappropriate prescribing is observed among prescribers, regulatory agencies may impose restrictions on specific drugs (or) on practitioners.

4. Facilitation of Pharmacoeconomic evaluations:

Data from PEY studies are often wont to measure the consequences of medicine on overall healthcare costs & resource consumption.

Ex: Hospitalization thanks to serious adverse effects of a drug results in more expenses also as resource consumption, which might be avoidable.

9. What is cost utility analysis. Explain with suitable examples how the outcome measured using cost utility analysis.

- Cost-utility analysis (CUA) is a method for comparing treatment alternatives that integrates patient preferences and Health Regulated Quality of Life (HRQOL)
- HRQOL measure is a utility, having value between 1.0 (perfect health) and 0.0 (death).
- Quality-adjusted life years (QALYs) are then derived by multiplying the time in a health state by the appropriate utility score.
- In CUA. Cost is measured in dollars, and therapeutic outcome is measured in patient-weighted utilities rather than in physical units.
- This method is well suited to the evaluation of chronic diseases that have deleterious effects on HRQOL
- Differences between treatments are expressed as the incremental cost per QALY gained.
- CUA can compare cost, quality, and the quantity of patient-years.
- Results of CUA are expressed in a ratio, a cost-utility ratio (C: U ratio).
- CUA is complex, and thus CUA can be limited in scope of application from a hospital or MCO perspective.
- CUA is employed less frequently than other economic evaluation methods because of a lack of agreement on measuring utilities, difficulty comparing QALY's across patients and populations, and difficulty quantifying patient preferences.
- In CEA, the costs are measured in money and there is a defined outcome. But in CUA, the outcome is an unit of utility (e.g. a QALY).

Calculating QALYs (Example)

With treatment X

- Estimated survival = 10 years
- Estimated quality of life (relative to 'perfect health') = 0.7
- QALY's = (s10 X 0.7) =7.0

Without treatment X

- Estimated survival = 5 years
- Estimated quality of life (relative to 'perfect health') = 0.5
- QALYs = (5X o.5) 2.5

QALY gain from treatment X = 7 - 2.5 = 4.5 QALY's

If the cost of treatment X is 8,000 then the cost per QALY Is 4,000 per QALY (8,000 divided between 4.5 additional QALY's)

Strengths and Limitations of CUA Strengths

¬Combines more than one measure of effectiveness

¬Combines both measures of mortality and morbidity into a single measure Limitations ¬Absence of agreement in measuring utilities

¬Results are often difficult to reproduce among different evaluators because of variations in methodologies to elicit diease weights

¬Problems with the quantification of patient problems

Limitations of QALYs and DALYs

¬ Does not capture wider effects that stem from interventions: e.g. impact on carers and family, non-health effects such as economic and social consequences

¬Social preference weighting and discounting of DALYs present certain ethical issues • Are young adults and non-disabled more productive • Does the value of health decrease over time?

10. What is cost effective analysis. Explain with suitable examples how the outcome measured using cost effective analysis.

- The most commonly employed method is cost-effectiveness analysis.
- Measures effectiveness (health benefit) in natural units (e.g. years of life saved, ulcers healed) and the costs in money.
- It compares therapies with qualitatively similar outcomes in a particular therapeutic area. For instance, in severe reflux oesophagitis, using a proton pump inhibitor compared to using H2 blockers.

- CEA does not allow comparisons to be made between two totally different areas of medicine with different outcomes.
- The results of CEA are expressed as a ratio either as an average cost-effectiveness ratio (ACER) or as an incremental cost effectiveness ratio (10ER).
- An ACER represents the total cost of a program or treatment alternative divided by its clinical outcome to yield a ratio representing the dollar cost per specific clinical outcome gained independent of comparators.

Average cost effectiveness (ACER) = Net Cost / Net Health Benefit.

- The key measure of CEA is the incremental cost effectiveness ratio **(ICER).**
- Incremental Cost Effectiveness Ratio =

$$\frac{\textbf{(Cost of drug A - Cost of drug B)}}{\textbf{(Benefits of drug A - Benefits of drug B)}}$$

- **ICER =** $\frac{\textbf{Difference in costs (A-B)}}{\textbf{Difference in benefits (A-B)}}$

- CEA is being used to set public policies regarding the use of pharmaceutical products (national formularies) in countries such as Australia, New Zealand, and Canada.

	COST OF THERAPIES	
	DRUG A	DRUG B
COSTS		
Acquisition	300	400
Administration	50	0
Monitoring	50	0
Adverse effects	100	0
Subtotal	500	400
OUTPUTS		
Extra years of life	2.22	1.6
Cost-effectiveness ratio	500/2.22 = Rs.225.	400/1.6 = Rs.250
	Per extra years off life	

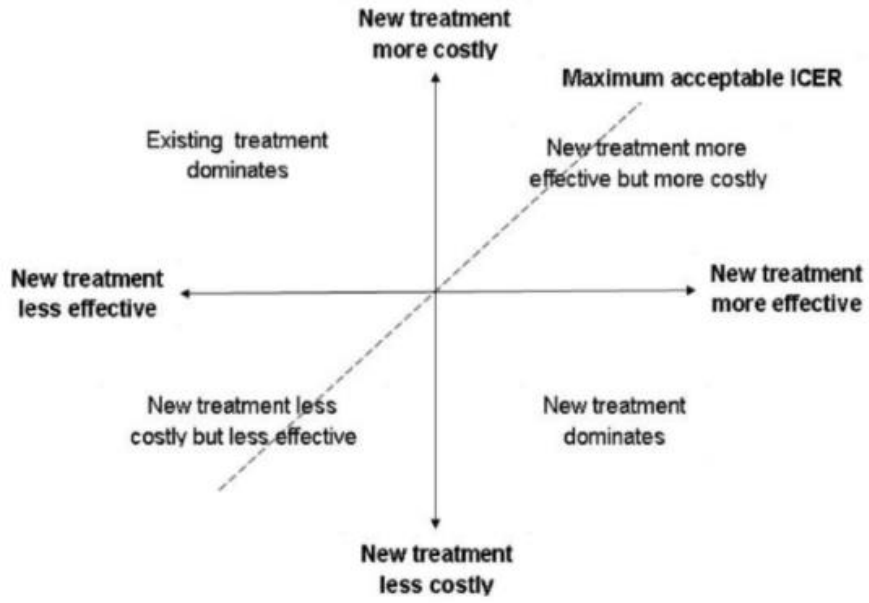
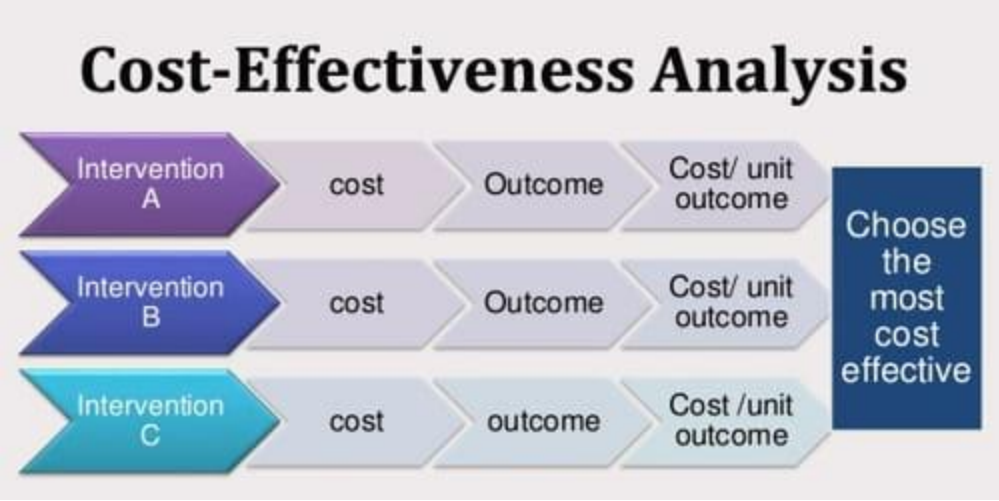


Figure 1: Cost-Effectiveness Plane



Incremental (or Marginal) Cost-Effectiveness Ratio

- The decision makers need to compute incremental (or marginal) cost-effectiveness ratios.
- This need arises when a new alternative is compared with the existing situation.
- The numerator now contains the difference between the cost of the new and old alternatives, and the denominator is also the difference between the effectiveness of the new and old alternatives:

$$\text{Marginal CE}_i = \frac{C_i - C_O}{E_i - E_O}$$

- This ratio can be interpreted as the incremental cost per unit of effectiveness. When there are several alternatives available, the marginal cost-effectiveness ratio can be used to rank the new measures versus the existing one.

Limitations of CEA

1. Does not measure willingness to Pay

- CEAs are a poor measure of consumers' willingness to pay as the output or benefit is not priced in the market nor is the output considered homogeneously.
- What is the willingness to pay for the additional "drug addicts treated"?
- The number of addicts treated may not be the best approximation of the value of the final outcome (i.e., consequential crime reduction may also be important for the taxpayers).
- The link between the intermediate measure of effectiveness and final output, such as reduction in crime, is not explicitly stated.
- Faced with this kind of situation, the analyst must make sure that this link is properly established. Even with this link, it is hard to know the value of the final outcome if no market value is placed.

2. Excludes some external benefits

The concept of CEA excludes most externalities on the benefits side.On the benefit side, the CEA looks only at a single benefit and all other benefits are essentially ignored.An improvement in education will not only increase life-time earnings of the students but also contribute to a reduction in the rates of unemployment and crime.In healthcare, there are external benefits due to such treatments as the vaccination of children, i.e. other people do not catch the infection diseases.The above issue will not occur for a complete CBA. The analyst doing the CEA should be careful not to exclude important benefits arising from a particular project.

3. Excludes some external costs

While computing the cost-effectiveness ratio for a particular project, attention is paid to the treatment of costs, which should include not only financial but also social costs.In the education sector, the enhancement of primary schooling is sometimes viewed in terms of the additional number of school blocks and improvement of

their physical conditions. Many other costs must be included to get the desired outcome.Different types of projects often have some of the costs in non-monetary terms, such as waiting time, coping costs, enforcement costs, regulatory costs, compliance costs, etc.The economic CEA carried out for such projects must account for all costs based on the economic instead of financial prices of goods and services.

4. Does not account for scale of project

Scale differences may distort the choice of an "optimal" decision.A project with smaller size but higher efficiency level may get accepted, while another project may provide more quantity of output at a reasonable cost.A strict CEA fails to overcome this problem.A complete CBA does not have this problem because the net present value already accounts for the differences in size among alternative projects.

11. Explain criteria for causal nature of an association in pharmacoepidemiology study

Association may be defined as the concurrence of two variables more often than would be expected by chance. Epidemiological studies determine various associations between an exposure and a disease. Further, its important to find out whether the exposure is causal for the disease or not.

Types of association
•Spurious association
•Indirect association
•Direct (causal) association
a) One-to-one causal association
b) Multifactorial association

Criteria for Causal Association Bradford Hill's criteria for making causal inferences- 1.Strength of association
2.Dose-Response relationship
3.Lack of temporal ambiguity
4.Consistency of findings
5.Biologic plausibility
6.Coherence of evidence
7.Specificity of association

1.**Strength of association**
• Measured by the relative risk (or odds ratio). • The stronger the association, the more likely it is that the relation is causal. • Relative risk is the ratio of the incidence of the disease among exposed and the incidence among non-exposed.
Example- Risk for development lung cancer 8.6 times higher in smokers than in non-smokers.

2.Dose-Response relationship
• As the dose of exposure increases, the risk of disease also increases • If present, it is strong evidence for a causal relationship. • Absence of a dose-response relationship does not necessarily rule out a causal relationship. • In some cases in which a threshold may exist, no disease may develop up to a certain level.
-

3.**Lack of temporal ambiguity**
• Exposure to the factor must have occurred before the disease developed • The temporal relationship is important in regard to the length of the interval between exposure and disease • It's easier to establish a temporal relationship in a prospective cohort study than in a case-control study or a retrospective cohort study.

_Example- Consumption of contaminated food should precede the symptoms of food poisoning.

4.**Consistency of findings**
• The relationship should be found consistently in different studies and in different populations. • Unless there is a clear reason to expect different results, replication of the findings should be there.

5.Biologic plausibility
• Biologic plausibility refers to coherence with the current body of biologic knowledge • Epidemiologic findings should be consistent with existing biologic knowledge. • Example- Carcinogens from cigarette smoke deposits in the lung over a period of time leading to lung cancer.

6.Coherence of evidence • If a relationship is causal, we would expect the findings to be consistent with other data. • For the appraisal of causal significance of an association it should be coherent with known facts that are thought to be relevant.
_Example- Peptic ulcer disease • Prevalence of H.pylori is same in men as in women. Incidence of duodenal ulcer in both have been proved to be equal in recent years. • Prevalence of peptic ulcer disease is believed to have peaked in the latter part of 19th century cause of poor living standards.

7.Specificity of association • Association is specific when a certain exposure is associated with only one disease • When specificity of an association is found, it provides additional support for a causal inference • Absence of specificity in no way negates a causal relationship.
_Example- Prevalence of H.pylori in patients with duodenal ulcer is 90% to 100%. However, it is found even in some patients of gastric ulcer and even in asymptomatic individuals.

_**Few other criteria which might be useful are**:
• Cessation of exposure- Risk of the disease declines when exposure to the factor is reduced or eliminated.
• Consideration of alternate explanations- Extent to which the investigators have taken other possible explanations into account and the extent to which they have ruled out such explanations are important considerations.

13. Explain in detail the measurement of outcomes in PE studies and explain in detail the drug use measures?

Outcome measurement: it's defined because the systematic quantitative chemical analysis of the result indicator at some extent of your time .
• These measures are wont to determine whether the goal of the patient, are identified and achieved.
measurement of outcomes are often done by two approaches:
1. Statistical Methods
2. Drug use measures.
1. Statistical Methods
(a) Prevalence
(b) Incidence
1. Cumulative incidence
2. Incidence rate (or) Incidence density

(a) Prevalence:

• It is that the proportion of individuals affected with a disease (or) exposure to a specific drug during a population at a "specific point (or) period of time".
• It is typically determined by surveying the population of interest.
• Prevalence varies between 0-1; it are often expressed as percentage.
• It may be a census sort of measure, indicating how frequently a disease is at a period of your time .

Uses

• Estimate the magnitude of health (or) disease problem within the community.
• To identify the potential high risk population community.
• It is particularly useful for administrative and planning purpose.
• Mathematically, Prevalence = A/B

A = no. of population with disease at a given time.
B = Total no. of population at a given time.

• Ex: If there are 1000 patients with epilepsy during a district of 10, 00,000 population.

Then prevalence of epilepsy = 1000/10, 00,000 = 0.001%

(b) Incidence:

Definition: it's a measure of the danger of developing some "new condition" within a selected period of your time .

In the case of descriptive studies two measurements of incidents are commonly used:

1. Cumulative incidence
2. Incidence density or incidence rate

Cumulative incidence

• It may be a number of latest cases within a selected period of your time , divided by the dimensions of population initially in danger .
• It is employed for the measure of the danger of disease or probably probability of developing the disease during specified period.
• Normally it's measured with an Inception cohort i.e. an outsized group of population is observed over a period of your time , and therefore the number of cases or outcomes is measured.

No. of latest cases of disease (or) injury during specified period
Size of population at start of period

Example: If a population initially contains 1000 non disease persons & 28 develop a condition over two years of observation, the incidence proportion is 28 cases per 1,000 persons.

Incidence rate

• It is that the number of latest cases per population in danger during a given period of your time .
• It describes the probability of a replacement case occurring during a given interval (or) how quickly disease occurs during a population.
• It may be a measurement combining the amount of persons and their time contribution (years, months or weeks) during a study.

Number of latest cases of disease (or) injury during specified period.
Total time everyone was observed (totaled for all persons)

Relationship between prevalence and incidence:

P = I x D
D = Duration.

It shows, longer the duration of the disease, greater the prevalence.

2. Drug use measures:

1. Monetary units.
2. Number of prescriptions.
3. Units of medicine dispensed.
4. Defined daily doses (DDD).
5. Prescribe daily doses (PDD).
6. Medical adherence measurement.

1. Monetary units

• Drug use has been measured in monetary units to quantify the amounts being consumed by population.
• It can indicate the burden on society from drug use.
• Monetary units are convenient and may be converted to a standard unit, which then allows for comparison.
• The disadvantage is quantifies of drug actually consumed, aren't known and costs may vary widely.

2. Number of prescriptions:

• It has been utilized in research, thanks to the supply and ease.
• Prescription number analysis is employed to urge rough estimates like percentage of analgesic drugs, oral contraceptives or antibiotics employed by the population,
• It helps to offer comparatively good estimates of number of individuals expose you to a particular drug. These sorts of studies also help to seek out whether there's increase within the number of prescriptions during certain periods.

3. Units of drug dispensed:

• Units of medicine represent measures like number of capsules (or) tablets (or) tablets (or) doses of vaccines.
• It is straightforward to get and may be wont to compare usage trends within population.
• Helps to research drug use trend in various countries, states (or) territories of country.
• Helps to match the hypothesis generated associated with drug use, like overuse (or) under use.
• It has limitations like units of medicine dispensed needn't always reflect the particular number of medicine employed by the population. people might not use certain dispensed medicines for various reasons.
• Hence, difficult to work out the particular number of patients exposed to the drug.

4. Defined daily doses (DDD):

• According to WHO, the DDD is that the assumed average maintenance dose per day for a drug for its main indications in adults.
• It is generally expressed as DDD/1000 Patients/day (or) DDD/100 bed/day.

Example: A patient has taken paracetamol as painkiller. it's having DDD = 3g i.e. average patient who uses paracetamol uses 3g during a day (or) within a period of 24 hours.
This is like 6 standard tablets of 500mg each. If patient consumes 24 such tablets.

$$\frac{24 \times 500}{3}$$

DDD = 4

Advantages:

• It is useful in describing and comparing patterns of drug use and provides denominator data for estimation of adverse drug reaction rates.
• It allows comparisons between drugs within the same therapeutic class.

Disadvantages:

Problems arise when doses vary widely like with antibiotics (or) if the drug has quite one major indication.
Ex: Aspirin: Low dose for cardiac events.
Moderate dose for pain management.

High dose for inflammatory conditions.
Pediatric uses are often not considered within the calculation.

5. Prescriber daily doses

- It is that the average daily dose of a drug that has actually been prescribed.
- It is calculated from representative samples of prescription.
- Prescriber daily dose is beneficial for validating that defined daily doses (DDD).
- Pharmaco-epidemiological information is additionally important so as to interpret a prescriber daily dose.

Prescriber daily dose can vary consistent with both the illness treated and national therapeutic traditions.

- Prescriber daily doses, also vary substantially between different countries and this could be considered while making international comparisons.
- Disadvantage is that it doesn't indicate no. of population exposed to drug.

6. Medical adherence measurements

I. Biological Assays
II. Pill counts
III. Weight of topical medications
IV. Electronic monitoring
V. Patient interviews

14. Explain in detail the concept of risk and measurement of risk of an ADR with respect to

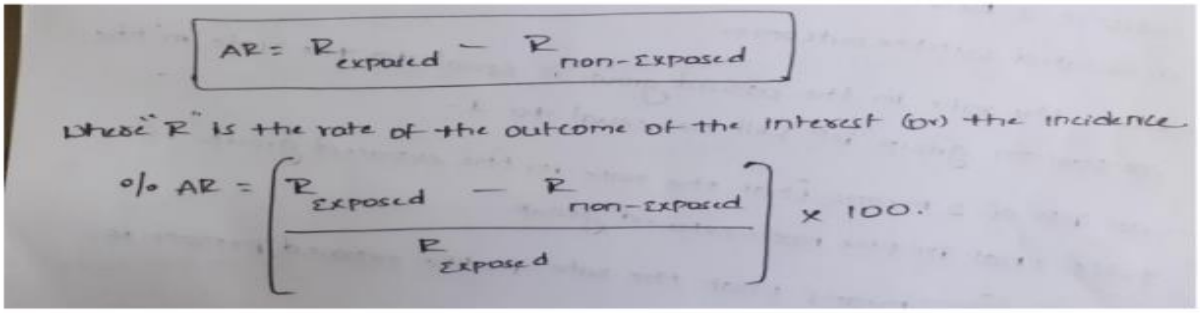
Attributable risk

ATTRIBUTABLE RISK

- It is additionally called Rate difference or Risk difference.
- Attributable risk is that the "difference in rate of a condition" between an exposed population and an unexposed population.
- Mostly calculated in cohort studies, where individuals are assembled on exposure status & followed over a period of your time .
- Then, the investigators count the occurrence of the disease.
- The cohort is then subdivided by the extent of exposure and therefore the frequency of disease is compared between subgroups.
- One is taken into account exposed & another unexposed.

$$AR = R_{exposed} - R_{non\text{-}exposed}$$

Where "R" is the rate of the outcome of interest (or) incidence.



- The risk of a drug has to be assessed with in the environment (or) atmosphere where it is used.

Example: We cannot attribute all incidence of GI discomfort in people taking Ampicillin capsules to the drug since some may have it for reasons than the drug.

Time risk relationship

TIME RISK RELATIONSHIP

- The outcome of an exposure to a drug is related to the time.
- It is also true, with risks associated with medicines.
- There is always a time related association of risk in Pharmacoepidemiology.
- Certain events like anaphylactic reactions happen immediately after taking an injection, while certain other risk events occur after days (or) months (or) even years.
- Ex: Prazosin, an alpha blocker has main effect in dilation of veins and arteries which leads to reduction in blood pressure. It is sometimes also used for BPH. To minimize the impact of first dose effect, Prazosin is normally taken at bedtime. Other drugs of same family, doxazosin & terazosin, can also cause this phenomenon, though less frequently.
- Delayed reactions to medications commonly begin more than 6 hours after exposure but sometimes occur days after exposure.

Ex:

- Delayed Adverse drug reactions to amoxicillin classically starts between 7 to 10 days of exposure and may even begin 1 to 3 days after the patient has stopped taking the medicine.
- Medications that cause delayed reactions include heparin, Quinine, Sulfonamides, vancomycin, gold compounds, beta lactam antibiotics and NSAIDs.
- The above mentioned aspects of medicine demonstrate that the exposure time must always be considered and the risk should be expressed as a function of time wherever possible in pharmacoepidemiology.

16. .Explain in detail the methods of Pharmacoeconomic evaluation.

(a) Cost of illness evaluation.

Cost of illness analysis is **a way of measuring medical and other costs resulting from a specific disease or condition**. For example, heart disease in the United States costs more than $321 billion each year—$193 billion in direct medical costs and $128 billion in lost productivity from early death.

Cost of illness (COI), known as burden of disease (BOD), is a definition that encompasses various aspects of the disease impact on the health outcomes in a country, specific regions, communities, and even individuals. The category of COI can range from the incidence or prevalence of disease to its effect on longevity, morbidity along with the decrease in health status and quality of life (QoL), and financial aspects including direct and indirect expenditures that result from premature death, disability or injury due to corresponding disease and/or its comorbidities.

The fundamental goal of COI study is to evaluate the economic burden that illness imposes on society as a whole. As explicitly stated in Jefferson et al. (2000), "the aim of COI studies is descriptive: to itemize, value,

and sum the costs of a particular problem with the aim of giving an idea of its economic burden." The COI studies traditionally stratify costs into three categories-direct, indirect, and intangible costs.

(b) Cost of minimization analysis.

• Cost-minimization analysis is that the most elementary technique.
• Cost-minimization analysis (CMA) involves the determination of the smallest amount costly alternative when comparing two or more treatment alternatives.
• The two alternatives must be equivalent therapeutically
• Once this equivalency in outcome is confirmed, the prices are often identified, measured, and compared in monetary units (dollars).
• CMA may be a relatively straightforward and straightforward method for comparing competing programs or treatment alternatives.
• CMA shows only a "cost savings" of 1 program or treatment over another.

For example:

• If drugs A and B are antiulcer agents equivalent in efficacy and adverse drug reactions (ADRs), then the prices of using these drugs might be compared using CMA.
• Another example would be prescribing a generic preparation rather than the brand leader.

Benefits:

• Simple method

Limitations:

• Outcomes must be equivalent for analysis.

(c) Cost of benefit analysis.

• Cost-benefit analysis (CBA) may be a method that permits for the identification, measurement, and comparison of the advantages and costs of a program or treatment alternative.
• The benefits realized from a program or treatment alternative are compared with the prices of providing it.
• Both the prices and therefore the benefits are measured and converted into equivalent dollars within the year during which they're going to occur.
• These costs and benefits are expressed as a ratio (a benefit-to-cost ratio), a net benefit, or a net cost. A clinical administrator would choose the program or treatment alternative with the very best net benefit or the best benefit-to-cost (B: C) ratio.
• If the B: C ratio is bigger than 1, the program or treatment is useful . the advantages realized by the program or treatment alternative outweigh the value of providing it.
• If the B: C ratio equals 1, the advantages equal the value . the advantages realized by the program or treatment alternative are like the value of providing it.
• If the B: C ratio is a smaller amount than I, the program or treatment isn't economically beneficial. the value of providing the program or treatment alternative outweighs the advantages realized by it.
• CBA should be used when comparing treatment alternatives during which the prices and benefits don't occur simultaneously.
• CBA can also be wont to evaluate one program or compare multiple programs.
• However, valuing health benefits in monetary terms are often difficult and controversial. The expression of some health benefits as monetary units is neither appropriate nor widely accepted.
• Therefore, unless the advantages of a program or treatment alternative are expressed appropriately in dollars, CBA shouldn't be used .

Advantages:

• Decision making.

Disadvantages:

- Over-simplistic.
- CBA is difficult to perform because it requires both cost and benefits to be measured in monetary terms.
- Productivity and quality of life is difficult to perform reliably and meaningfully.

	COST OF THERAPIES	
	DRUG A	DRUG B
COSTS		
Acquisition	300	400
Administration	50	0
Monitoring	50	0
Adverse effects	100	0
Subtotal	500	400
BENEFITS		
Days at work($)	1000	1000
Extra months of life($)	2000	3000
Subtotal	3000	4000
Cost-output ratio	3000/5000	4000/400
	6:1	10:1

18. Define record linkage system and explain the process of record linkage system and also explain the probabilistic and deterministic approach in record linkage system?

NEED FOR RECORD LINKAGE

- Researchers and therefore the community's demand for detailed statistical information.
- In response to increasing business and health needs.
- Improving data quality and timeliness.
- In reducing the complexity of knowledge .
- Reducing respondent burden and costs.

What is Record Linkage?

- Record linkage is that the process of bringing together two or more records concerning an equivalent individual (person), family or entity (e.g. event, object, geography, business etc.).
- To find syntactically distinct data entries that ask an equivalent entity in two or more input files.
- Part of the info cleaning process, which may be a crucial initiative within the knowledge discovery process.

DETERMINISTIC RECORD LINKAGE:

- A pair of records is claimed to be a link if the 2 records agree exactly on each element within a set of identifiers called the match key.
- ALL or NONE
- For example, when comparing two records on surname , street name, year of birth, and street number, and therefore the pair of records is deemed to be a link as long as the names agree on all characters, the years of birth are an equivalent , and therefore the street numbers are identical.

PROBABILISTIC RECORD LINKAGE:

• Formalized by Fellegi and Sunter [1969].
• Pairs of records are classified as links, possible links, or non-links.
• Here, we consider the probability of a match within the given observed data.
• In probability matching, a threshold of chances are set (which are often varied in several circumstances) above which a pair of records is accepted as a match, concerning an equivalent person, and below which the match is rejected.

STANDARDIZATION:

• In every data there exist many manual errors and non-matching abbreviations etc. which can present themselves as separate data without actually being so
• First step : to wash and standardize the info
• E.g.: For input file belonging to Mr. William Marcus Smith, entries could are made by different individuals as:

- Smith W. M.
- William M. Smith
- W.M. Smith
- W.M. Smithe etc.

BLOCKING:

• In order to scale back the search space (i.e. the amount of record pairs to be compared).
• To group similar records together, called blocks or clusters.
• The data sets are split into smaller blocks and only records within an equivalent blocks are compared.
• E.g. rather than making detailed comparisons of all 90 billion pairs from two lists of 300,000 records representing all businesses during a State of the U.S., it's going to be sufficient to think about the set of 30 million pairs that agree on U.S. Postal postcode .

MATCHING

Exact Matching:

• Linkage of knowledge for an equivalent unit (e.g., establishment) from different files.
• Uses identifiers like name, address, or tax unit number.

Statistical Matching:

• Attempts to link files which will have few units in common.
• Linkages are supported similar characteristics instead of unique identifying information.

Requirements for outlining a RLS:

• The sorts of linkages required, whether the linkages is performed in batch and/or interactive mode.
• The security provisions for confidential data files.
• The speed of operation needed.
• The volume of records which will be linked with the system.
• The initial cost of software including licensing and maintenance costs.
• Whether the software is bundled with other software packages.
• The simplicity and adaptability in defining the principles used for linkages.
• The accuracy and statistical defensibility of the merchandise .
• The availability of documentation and training, and
• The maintenance and support of the software.

USES

• The system is employed to enhance data quality and coverage, for future medical follow from cohorts, for creating patient-oriented instead of event-oriented data, for building new data sources, and for a variety of other statistical purposes.
• It helps create statistically relevant source of 'new' information.

• Answers research questions concerning genetics, occupational and environmental health and medical research.

DRAWBACKS

• Issues of privacy and confidentiality.
• Policies for conducting studies using such systems must be transparent.

APPLICATIONS

• Duplication in data in minimized.
• Powerful tool for generating more value out of existing databases.
• Large projects regarding the census of a whole country are often planned.
• More detailed information are often obtained.
• Becomes easier to follow cohorts.

26. Explain few important pharmacoepidemiological studies involving drug induced birth defects

TESTING FOR TERATOGENICITY

• Standardized procedures for testing drugs for teratogenic potential are used.
• They use a minimum of two common mammalian laboratory species that are given several different doses of the test agent once or several successive days during organogenesis and early fetal period.
• Conventionally 3 doses are administered; the very best causing maternal toxicity.
• Evaluation of human case reports and epidemiological investigation (retrospective & prospective).
• About 80% pregnant women use prescribed or over-the-counter drugs.
• The drugs should only be taken when essential thereby avoiding unnecessary and unknown risks.
• The same is clearly applied to social drugs like tobacco, alcohol and additive drugs.

PROCESS OF ASSESSING REPRODUCTIVE OR EMBRYO/FETOTOXIC EFFECT OF DRUG

- A sudden increase in the prevalence of a specific malformation is observed.
- An association is established between the introduction or an increased usage of a drug and an increased prevalence of a specific malformation.
- Drug use must be taken place in the sensitive period for the introduction of that specific malformation.
- Drug or its metabolite suspected of causing malformation has to be proved capable of reaching the embryo or fetus.
- It must be established that the drug and not condition (disease) causes the specific malformation.
- The findings have to be confirmed by another independent study.
- The result of specific laboratory animal studies might support the epidemiological findings.

SURVEILLANCE AND MONITORING

- International Clearinghouse of Birth Defect Monitoring Systems (1974).
- EUROCAT (European Concerted Action on Congenital Abnormalities and Multiple Births -1979).

TERATOLOGY INFORMATION SERVICES

Teratology Information Services (TIS) provide information on the possible risks of exposure to drugs and other exogenous agents during pregnancy and lactation. Teratology Information Services are consulted by the medical profession and other health care professionals, some of them counsel lay people as well. Answers provided are specifically oriented towards individual patients. Detailed knowledge of dose, time of exposure, adverse effects on the mother related to the exposure, diseases, previous pregnancies, family history of the patient and the pharmacological and toxicological properties of the agents have to be taken into account to make a specific risk assessment.

A TIS deals with the following types of inquiries:

- **BEFORE PREGNANCY:**
  - A couple is planning a pregnancy and is being exposed to drugs/chemicals. What is the risk? Should this exposure be changed or stopped? Does this exposure decrease fertility?

- **DURING PREGNANCY:**
  - A pregnant woman has taken a drug before she realizes that she is pregnant. What is the risk? Would recommending termination of pregnancy be justified? What prenatal diagnostic procedures can be offered?
  - A drug has to be prescribed to a pregnant woman. Is it safe? Is there a less toxic/teratogenic drug with comparable therapeutic efficacy to which the woman should be transferred? Is the risk of taking a drug greater than the risk of the disease for which the drug is taken? Are there risks acceptable to the patient when compared with the spontaneous risk of developmental disorders?

- A pregnant woman has attempted to commit suicide by taking an overdose of a drug.
- What information should be given to the physician at the emergency department? Can the appropriate antidote be given to her?
- A pregnant woman is addicted to drugs/alcohol. Do they have an adverse effect on the course of pregnancy? What are the effects on fetal development? Can neonatal problems be expected or are there any long-term consequences for the child?
- A pregnant woman is exposed at work to certain chemicals. What is the risk? Should she continue this work?
- A pregnant woman is exposed to an infectious agent. What are the risks of a maternal infection for the fetus? Are techniques available for the diagnosis of a fetal infection and what are the management options? Similar questions are made for non-infectious maternal diseases.
- A pregnant woman has been exposed to... What are the risks of certain physical exposures such as heat and radiation (especially x-rays and radioactive materials), vaccinations or environmental pollution?
- A man has been exposed to chemicals or has been treated with d rugs. Are there any paternally mediated risks for the fetus or baby?

- **AFTER PREGNANCY:**

- A baby is born with a birth defect or a neonatal disorder.
- Can this be attributed to a drug or chemical to which the mother was exposed before or during pregnancy?
- A drug has to be prescribed to a mother while she is breastfeeding. A mother uses a prescription drug or is exposed to another exogenous agent, while breastfeeding.
- What is the (relative) dose the neonate (infant) is exposed to?
- Is this acceptable for its age?
- What is the treatment of choice during breastfeeding?

SHORT ESSAYS 05 MARKS

3. What is Markov model. Explain with examples.

Markov Models

Many clinical conditions involve recurring events at uncertain times over the lifetime of an individual. For interventions targeted towards these conditions, a decision tree is less suitable as it would become unwieldy if it had to represent all possible sequences of events over a lifetime (or alternative time horizon). For example, consider individuals with high cholesterol levels who are at increased risk for coronary heart disease. If we used a decision tree to evaluate the use of statin therapy for these patients we would have to specify a fixed time horizon. For example, we could model the likelihood of having coronary heart disease at 10 years and the likelihood of dying (from any cause) under the "treat" and "no treat" scenarios. However, this framework would not capture when the disease or death occurred within the 10-year time frame, which may be important. It would also not capture any events that may occur beyond 10 years. Hence, Markov models are ideal for modeling clinical problems that involve risk over time, or when the timing of events is important. Markov models consist of a defined set of mutually exclusive and collectively exhaustive health states, where a cohort of simulated individuals resides over time. Markov models also provide a useful tool for calculating life expectancy, as that is often an outcome in interest in medical decisionmaking. For example, simple Markov models can extend the time horizon of a decision tree with the sole purpose of calculating life expectancy with a

two-state model ("alive" and "dead" states) using annual probabilities from a life table or adjusted life table. As with a decision tree, a Markov model can be computed either analytically to obtain the expected values of the outcomes or stochastically (i.e., where the outcomes are sampled) to obtain a measure of variability in health outcomes in addition to the expected value.

The advantage of using a Markov model is that this relatively standard modeling approach can capture many of the features present in a clinical process, such as risk of disease over time, changing health states over time and episodic events. The primary disadvantage is the underlying assumption that the probability of moving from one health state to another only depends on being in that state and does not depend on past history, either states visited in the past or time spent in that state. This assumption is known as the Markovian property and can be a very limiting assumption for clinical applications. The way that modelers get around this "memoryless" property is to create health state descriptions that include past history. For example, health states can be defined according to whether a stroke has occurred in the past, or perhaps even the number of or type of stroke. Health states can also be defined to include the number of years spent in a particular state. The impact of this is that the number of states can increase exponentially as the analyst attempts to include all of the relevant history for a clinical problem, which can result in a very large model that is difficult or sometimes impossible to manage.

3. Describe studies of vaccine safety.

A vaccine may be a biological preparation that improves immunity to a specific disease.
• Vaccines are among the foremost cost-effective and prevalent public health interventions.
• Morbidity & mortality declined where immunizations are practiced.
• Vaccine safety is prime for

1. Public
2. Manufacturer
3. Immunization providers
4. Recipients of vaccines

METHODS OF MONITORING VACCINES SAFETY
There are two methods of monitoring vaccines:
¬ Pre-licensure
¬ Post-licensure
PRE -LICENSURE MONITORING
• Vaccines like other pharmaceutical products, undergo extensive safety and efficacy evaluations within the laboratory.
• Pre-licensure studies are administered on :
¬ Animals.
¬ Humans.
Pre-licensure Human Studies:
• Phases I, II, Ill trials.
• Common reactions are identified.
• Vaccines are tested in thousands of persons before being licensed and allowed on the market.
Most trials involve patients but screening and prevention trials often recruit healthy volunteers.
Phase-I: This stage checks that the treatment is safe and finds the simplest dose to use.
Phase-II: This stage tests how well a test or treatment works.
Phase-III: This stage compares the new treatment with the present treatment. These are large scale trials.

POST-LICENSURE MONITORING
• Identifies rare reactions

• Monitor increases in known reactions
• Identify risk factors for reactions
• Identify vaccine lots with unusual rates or sorts of events
• Identify signals
• Phase IV studies are often an FDA requirement for licensure.
• These trials include tens of thousands of volunteers and should address questions of long-term effectiveness and safety or examine unanswered questions identified in phase III clinical trial clinical trials
• Manufacturers must submit samples of every vaccine lot and results of their own tests for potency and purity to the FDA before, releasing them for public use.

5. Explain the steps involved in cost minimization analysis study.

• Cost-minimization analysis is that the most elementary technique.
• Cost-minimization analysis (CMA) involves the determination of the smallest amount costly alternative when comparing two or more treatment alternatives.
• The two alternatives must be equivalent therapeutically
• Once this equivalency in outcome is confirmed, the prices are often identified, measured, and compared in monetary units (dollars).
• CMA may be a relatively straightforward and straightforward method for comparing competing programs or treatment alternatives.
• CMA shows only a "cost savings" of 1 program or treatment over another.

Following are the steps:
Obtain acquisition price for each medicine and calculate the price for the course of treatment to be compared- dose per day, number of days of treatment.

♦ Calculate pharmacy, nursing and physician cost associated with the use of each medicine.
♦ Calculate equipment cost associated with each medicine.
♦ Calculate laboratory costs associated with each medicine.
♦ Calculate cost of any other significant factor
♦ Calculate and compare total medicine costs for each medicine.

Example 1 Category Medicine A Medicine B Acquisition price USD 8.OO USD 15.00 Pharmacist salary USD 2.50 USD I.50 Nurses salary USD 2.50 USD 2.00 Supplies USD 9.00 USD 2.25 Lab services USD 4.00 USD 1.00 TOTAL USD 26.00 USD 21.75
Example 2 ♦ For example, we may wish to compare the cost of organizing communal days for periodic impregnation of mosquito nets with distributing individual kits for home use in order to find which of the two options is cheaper. The expected outcome is the treated net for both strategies. The study would now try to establish which of the two options is cheaper.

4. Explain the role of pharmacoeconomics in formulary management.

Pharmacoeconomic assessment of formulary actions has become increasingly common in local, national, and international formulary decision making. Tactics for managing medication use include formulary management and drug policies. Pharmacoeconomic data can provide support for these formulary decisions. For example, pharmacoeconomic data can support the inclusion or exclusion of a drug on or from the formulary and support practice guidelines that promote the most cost-effective or appropriate utilisation of pharmaceutical products. Various strategies can be used to incorporate pharmacoeconomics into formulary decision making. These include using published pharmacoeconomic studies and economic modelling techniques, and conducting local pharmacoeconomic research. Criteria

for evaluating the pharmacoeconomic literature, suggestions for employing economic models, and suggested guidelines for conducting pharmacoeconomic projects are discussed. Although most formularies are viewed as cost-containment tools, formularies should not be a list of the 'cheapest' alternatives. Today's formulary should contain agents that optimise therapeutic outcomes while controlling cost. Pharmacoeconomic assessments of formulary decisions help to ensure that the agents promoted by our formularies yield the highest outcome per dollar spent. A discussion of the process for formulary action in a US hospital, the influence of pharmacoeconomics on US formularies, and strategies for incorporating pharmacoeconomics into formulary decision making are presented in this paper.

6. Explain the factors to determine cost of illness study.

Cost of illness analysis may include direct costs, productivity losses, and intangible costs of a disease or injury. Direct costs from a disease or condition may include:

- **Medical costs**, such as the cost of diagnostic tests, physician office visits, and drugs and medical supplies
- **Non-medical costs**, such as travel costs for obtaining care and related childcare costs.
- **Productivity losses** include impacts of patient and caregiver participation in an intervention, such as work or leisure time lost due to participation in the intervention. These costs are generally more complicated to measure than direct costs.

- Direct components of household health costs

1. *General Practitioner services (public and private)	21. Receive services Cosmetic (skin care, hair)
2. *specialist physician services (public and private)	22. Public Health services, particularly maternal and child services (public and private)
3. general dentists services (public and private)	23. Elder care services (health related expenses)
4. Dentistry Prosthodontics services (public and private)	24. Premiums for basic health insurance mandatory
5. dental specialists services(public and private)	25. Basic health insurance premiums for voluntary

5. Non-physician personnel services (public and private)	26. Premiums for supplemental insurance
7. Traditional healing services (public and private)	27. Receiving rehabilitation services (including physiotherapy, speech therapy, optometrist, audiological and occupational therapy and prosthetics services)
3. Midwifery services (public and private)	28. * Receive diagnostic services (including laboratory, imaging and genetic counseling clinic)
9. Emergency services (public and private)	29. ***under the table payment, as money (voluntary / involuntary as a condition for receiving service)
10. Services received at home	30. ***Purchasing drugs that have been imported unofficial

indirect components of household health costs

1. expenses related to the patient's permanent disability due to illness	6. *Transportation expenses associated with patient family
2. expenses related to the patient's temporary disability due to illness	7. *Patient's family food expenses (in excess of the normal cost of food)(_In place of service receiving)
3. expenses related to the patient's family temporary disability	8. *Expenses related to patient's family housing (In place of service receiving)
4. expenses related to the patient's changing jobs	9. Expenses of information and communication technologies (telephone, Internet, etc.)
5. Expenses related to the patient's family changing jobs	10. Expenses resulting from the change in location due to illness of a family member

Intangible components of household health costs

1. *The pain of disease for the patient	23.*_Patient stress and anxiety concerning the economic problems and self-sufficiency disabilities
2.*Patient's family suffering due to patient's pain	24. Patient's family stress and anxiety concerning the occurring Economic self-sufficiency disabilities for patients
3. Patient Depression[1] due to disease	25. *, **_Patient stress and anxiety concerning the confusion in selecting a physician
4. patient's family_Depression	26. *, ** Patient's family stress and anxiety concerning the confusion in selecting a physician
5. *, **_patient's Stress[2] and anxiety[3] due to inability to pay health costs	27. Patient stress and anxiety concerning the selection of treatment center
6. *,** Patient's family stress and anxiety concerning the inability to pay for health costs	28. Patient's family Stress due to confusion in the selection of treatment center
7. Patient stress and anxiety concerning the behavioral disabilities[4] due to disease	29. patient stress resulting from loss of time due to long waiting lists
8. Patient's family stress and anxiety concerning the behavioral disability due to disease	30. Patient's family stress resulting from loss of time due to long waiting lists
9. Patient stress and anxiety concerning the Communication disabilities due to disease	31. * Stress imposed to the patient due to lack of confidence in the

7. How is confidence interval measured for an odds ratio.

Confidence level

The confidence level is the probability that the confidence interval contains the true odds ratio. If the study was repeated and the range calculated each time, you would expect the true value to lie within these ranges on 95% of occasions. The higher the confidence level the more certain you can be that the interval contains the true odds ratio.

The odds ratio (OR) is a measure of how strongly an event is associated with exposure. The odds ratio is a ratio of two sets of odds: the odds of the event occurring in an exposed group versus the odds of the event occurring in a non-exposed group.

Odds Ratio = (odds of the event in the exposed group) / (odds of the event in the non-exposed group)

If the data is set up in a 2 x 2 table as shown in the figure then the odds ratio is (a/b) / (c/d) = ad/bc. The following is an example to demonstrate calculating the odds ratio (OR).

- Upper 95% CI = e ^ [ln(OR) + 1.96 sqrt(1/a + 1/b + 1/c + 1/d)]

10. What is decision tree. With an example explain the use of decision tree in clinical decision analysis.

A decision tree provides a logical structure of the decision and possible events as they unfold over time. The decision tree is made up of series of nodes and branches, and begins with a decision node (represented by a square) with all of the branches off of this node representing the different options available to the decisionmaker, such as treat, no treat, or test. Following these branches one can represent the events that can happen (e.g., patient has a positive test result) and the various states of nature that exist (e.g., patient has the disease of interest, though this is unknown to the decisionmaker) by a series of chance nodes (represented by circles) and branches (representing events or states). The probabilities of events or states of nature dictate the chance of going down one branch versus another, and can be estimated from data. Decision nodes can be placed "downstream" to represent a decision that is made later; for example, the decision to do an additional test if the first test is negative.

The terminal nodes that are placed at the end of each of the possible pathways in the decision tree represent the outcome(s) of interest after a specified time horizon. The outcome or set of outcomes that is specified should represent what is important to the decisionmaker. A decision tree can be computed either analytically (called a "rollback analysis") to obtain the expected value of the health outcome associated with each strategy, or stochastically (i.e., where the outcomes are sampled) to obtain a measure of the variability in health outcomes in addition to the expected value. In some cases the outcome is very easy to quantify, such as whether the patient is dead or alive, that is, the optimal strategy will be the one that maximizes survival. For other cases the valued outcome is more qualitative in nature, such as levels of pain. Decision analysis, which includes the use of decision trees, uses utility theory or multiattribute utility theory to attach a value to all possible outcomes, which allows for a quantitative value to be assigned to a qualitative outcome in a manner that is consistent with the axioms of decisionmaking.[4] The quantification of qualitative outcomes is, indeed, one of the criticisms of the decision-analytic approach. Suppose treatment A resulted in equal chances of no, mild, or severe pain, and treatment B resulted in equal chances of no or severe pain, with no chance of mild pain. A decision to go with treatment A implicitly values mild pain closer to no pain, whereas a decision to go with treatment B values mild pain closer to severe pain. Such implicit value judgments must be made all of the time in health care. Decision analysis provides the tools to make them explicit and transparent to the decisionmaker.

The primary advantage of using a decision tree over the other types of models is that decision trees are easy to follow and laid out in a very logical and linear fashion. Even in cases where the decision tree is quite "bushy,"

the decisionmaker can view each of the possible pathways following an option, as well as the pathway probabilities. The primary disadvantage of a decision tree is that it is only applicable to situations where there are no (or very limited) recurring events and where the relevant time horizon is relatively short and fixed.

12. Describe the steps involved in formulating a study decision in pharmacoepidemiology.

Steps Involved in Designing a Study

- Outline of study
- Title of study
- Research question (what is the overall, broad question?)
- Research hypotheses (specific clear and sequential sets of questions to be addressed)
- Significance of the study—new data/confirmatory, and why is it important?
- Why should anyone other than the interested investigator spend time or resources in this proposal?
- Comprehensive description of study design
- Inclusion/exclusion criteria; how will participants be recruited?
- What outcomes and other factors will be measured—why and how?
- How will data be analyzed—describe how each variable will be handled; how missing information will be handled; sample size and power? What is an important difference to detect (10%, 25%, 5 inches, 10mm of something . . .)?
- How will the data be safeguarded (HIPAA compliance)?
- Potential problem areas—logistics (e.g., power outage—will biological samples be lost? safeguards?)
- Limitations of study and how can these be corrected?
- Is the study proposal approved (approval pending) by institutional IRB?

Potential Problems and Solutions in Designing Studies

- Research question is too broad/general (*Narrow the question; use smaller set of variables*)
- Not enough subjects available (*Broaden inclusion criteria; increase time*)
- Methods beyond investigator's skill level (*Collaborate, consult, learn*)
- Too expensive (*Consider less expensive alternatives, smaller study, less follow-up*)
- Question not interesting/novel enough (*Consult and discuss with mentors/peers; modify research question*)
- Uncertain ethical suitability (*Consult with IRB; modify research question*)
- Vague study plan (*Write proposal early and revise several times*)
- Proposal confusing/unclear (*Write proposal in point-by-point manner for specificity*)

13. What are the requirements of an ideal database. Write the strength and weakness of automated database.

14. Explain the benefits and limitations of a automated database

• Automated data may be a creation & implementation of technology that automatically process data.
• The technology includes computers & other electronic communications that gather, store, process, prepare & distribute data.
• The main purpose is, to quickly & efficiently process great deal of data with minimum human interaction.
• Various automated data sources are used world-wide for conducting pharmacoepidemiological research. a number of them are:

- Group Health Cooperative.
- Health Maintenance Organization (HMO) research network.
- Medicaid Databases.
- Kaiser Permanente medical aid Program.
- United Health Group. Etc.

IDEAL DATABASE

• Ideal database include records from:
1. Inpatient (IP) & Outpatient (OP) care.
2. Emergency care.
3. psychological state care.
4. All prescribed and OTC medications.
5. All laboratory and radiological tests, and
6. Alternative therapies.

• The population covered by the database would be large enough to allow discovery of rare events of medicine .
• The drug(s) under investigation must be present in formulary and must be prescribed in sufficient quantity to supply adequate power of study .
• Other requirements of a perfect database are that:
1. All parts are easily linked by means of a patient's unique identifier.
2. Records are updated on a daily basis.
3. Records should be verified and are reliable.

• Information on potential confounders like smoking & alcohol consumption may only be available through chart review (or) more consistently through patient interviews.

CLAIMS DATABASES

• Claims data arises from a person's use of the health care system.
• When a patient goes to a pharmacy and gets a drug dispensed, the pharmacy bills the insurance carrier for the value of that drug, and has got to identify which medication was dispensed, the milligrams per tablet, number of tablets, etc.
• Analogously, if a patient goes to hospital (or) to a physician for medical aid , the providers of care, bill the insurance carrier for the value of medical aid , and need to justify the bill with a diagnosis.

Medical record databases:

• MRD (medical record databases) are newer development arising out of the increasing use of computerization in medical aid .
• The validity of the diagnosis data in these databases is best than that in claims databases.

Advantages:

• Potentially provides large sample size.
• Relatively inexpensive to use.
• Data are often complete.
• Databases are population based, they will include OP drugs & diseases, & there's no opportunity for recall & interviewer bias.

Disadvantages:

• Uncertain validity of diagnosis data.

• Lack of data on some potential confounding variables.

Ex: Smoking, alcohol etc.

Group Health Cooperative:

• Data from health maintenance organization (HMO) has been used extensively to guage drug usage and therefore the adverse and beneficial effects of marketed drugs and medical procedures.

• GHC's may be a automated & manual database function a serious resource for several epidemiological studies, because individual records are often linked through time & across data sets by the unique consumer number.

HMO Research network:

• Research units in US HMO's are during a unique position to integrate research & practice for the development of health & health care among diverse population.

• It includes large sample size with a good range of comorbid conditions and concomitant medications to guage the beneficial and adverse effects of medicine .

United Health Group:

• These databases are used extensively to review drug safety and adverse drug reactions.

• United health group databases provide extensive data sources to review post marketing drug safety and to guage risk communication efforts.

15. Explain CMA and give its applications.

• Cost-minimization analysis is that the most elementary technique.

• Cost-minimization analysis (CMA) involves the determination of the smallest amount costly alternative when comparing two or more treatment alternatives.

• The two alternatives must be equivalent therapeutically

• Once this equivalency in outcome is confirmed, the prices are often identified, measured, and compared in monetary units (dollars).

• CMA may be a relatively straightforward and straightforward method for comparing competing programs or treatment alternatives.

• CMA shows only a "cost savings" of 1 program or treatment over another.

For example:

• If drugs A and B are antiulcer agents equivalent in efficacy and adverse drug reactions (ADRs), then the prices of using these drugs might be compared using CMA.

• Another example would be prescribing a generic preparation rather than the brand leader.

APPLICATION OF CMA

- In situations where the benefits of alternative treatments have been proven to be identical and as such this methodology is perceived as being easy to apply.
- It is used in supporting and justifying the introduction of cheaper drugs in the same therapeutic class.
- It is used when finding out the activity or output with the lowest cost

16. Write a note on prescription event monitoring

PEM may be a non-interventional, observational cohort sort of Pharmacovigilance.

• It is that the method of studying the security of latest medications employed by the overall practitioner.

Evolution of Prescription Event Monitoring:

• Pre-marketing clinical trials are effective in studying the efficacy of drugs but aren't ready to define many aspects of drug safety because:

1. Small no of patients.
2. Large no of patients receiving the drug for little durations.
3. Doses and formulations of the drug may change during drug development.
4. Exclusion of special population from the clinical trials.

• The contribution of spontaneous reporting system in detecting hazards like oculomucocutaneous syndrome with Practolol led to determine the system of Prescription event monitoring at DSRU.

• In New Zealand, the medicines adverse reaction committee (MARC) is liable for conducting such studies for tutorial purposes and therefore the program is understood as Intensive medicine monitor program (IMMP).

ADVANTAGES:

- Calculation of incidence density.
- Carried out on a national scale.
- Comparison of 'reasons for withdrawal' and incidence density.
- Outcome of exposed pregnancies.
- Signal generation and exploration.
- Delayed reactions are often detected.
- Disease investigation.

DISADVANTAGES:

- No method of measuring compliance.
- No method to work out the non-prescription medication.
- Non-return of green forms.
- Does not reach hospital monitoring.
- Data collection is an operational difficulty.

21. Define spontaneous reporting system.

• Spontaneous reporting system may be a passive closed-circuit television .

• Health professionals are encouraged to report adverse reactions which they believe to be drug-related directly to:

1. The regulatory authorities (or)

2. the corporate making the suspected product on a voluntary basis.

• Spontaneous reporting system has three steps:

1. Data Acquisition

2. Data assessment

3. Data interpretation

1. Data acquisition:

Which depends largely on the input of data derived from the reports submitted by the health professionals, who have encountered, what they think is an ADR.

2. Data assessment:

Involves assessment of the individual case reports and assessment of pooled data obtained from various sources, like the international database of the WHO.

3. Data interpretation:

supported the available data and assessments made, a sign associated with the adverse reaction could also be generated.

Pharmacovigilance aims at detecting adverse effects of marketed drugs. it's generally supported a spontaneous reporting system (SRS) that consists of the spontaneous reporting, by health professionals, of events that are alleged to the adverse effects of marketed drugs.

• Automated signal generation methods are proposed.

• The success or failure of any Pharmacovigilance activity depends on the reporting of suspected adverse reactions.

Different countries have different adverse drug reporting forms (or) systems. Those are:

• India - Suspected Adverse Drug reaction reporting form.

• UK - 'Yellow card' since 1964.

• Australia - 'Blue card' since 1964.

• United States - 'Med watch'.

• Form FDA 3500 - Voluntary reporting.

• Form FDA 3500A - Mandatory reporting.

Studies in pharmacoepidemiology are intended to be either "hypothesis generating" or "hypothesis testing".

Hypothesis-generating studies, with a recently marketed drug, aim to detect unexpected adverse drug reactions.

Hypothesis testing studies, aim to prove whether any suspicious which will are raised are justified.

Hypothesis - Generating studies:

They are generally done by two methods:

• Spontaneous ADR reporting.

• Prescription event monitoring (PEM).

SPONTANEOUS ADR REPORTING

• Spontaneous reporting is defined as "A system whereby case reports of adverse drug reactions or events are voluntary submitted by health professionals and pharmaceutical companies to the National Pharmacovigilance Centre" (NPC).

• Doctors (in some countries, other health care professionals and patients as well) are given forms, upon which, if they detect any suspected adverse drug reactions, they will notify it to the "central authority".

• In the uk , the 'yellow card' has been used for this purpose since 1964.

• The 'blue card' system is employed in Australia and Malaysia.

• In the us , the "Med watch" form is employed , and is formed broadly available to health professionals to encourage reporting.

24. What are meta analysis models. Give examples with strengths and weakness.

Definition of meta-analysis (from Glass, 1976): The statistical analysis of an outsized collection of study results for the aim of integrating the findings.

• The basic purpose of meta-analysis is to supply an equivalent methodological rigor to a literature review that we require from experimental research.

STEPS TO PERFORM META-ANALYSIS

1. Define the theoretical relationship of interest.
2. Collect the population of studies that provide data on the connection .
3. Code the studies and compute effect sizes.
4. Examine the distribution of effect sizes and analyze the impact of moderating variables.
5. Interpret and report the results.

USES

Meta-analysis would be used for the subsequent purposes.

• To establish statistical significance with studies that has conflicting results.
• To develop a more correct estimate of effect magnitude.
• To provide a more complex analysis of harms, safety data, and benefits.
• To examine subgroups with individual numbers those aren't statistically significant.

If the individual studies utilized randomized controlled trials (RCT), combining several selected RCT results would be the highest-level of evidence on the evidence hierarchy, followed by systematic reviews, which analyze all available studies on a subject .

Advantages:

- Greater statistical power.
- Confirmatory data analysis.
- Greater ability to extrapolate to general population affected.
- Considered an evidence-based resource.

Disadvantages:

- Difficult and time consuming to spot appropriate studies.
- Not all studies provide adequate data for inclusion and analysis.
- Requires advanced statistical techniques.
- Heterogeneity of study populations.

26. Explain the types of errors that can occur in a pharmacoepidemiological study.

ERROR: Definitions :

A false or mistaken result obtained in a study or experiment.

- Random error is the portion of variation in measurement that has no apparent connection to any other measurement or variable, generally regarded as due to chance.
- Systematic error which often has a recognizable source, e.g., a faulty measuring instrument, or pattern, e.g., it is consistently wrong in a particular direction (Last)

These errors are generally produced by one or more of the following:

- RANDOM ERROR • RANDOM MISCLASSIFICATION • BIAS • CONFOUNDING

- **Random error** • Deviation of results and inferences from the truth, occurring only as a result of the operation of chance. Can produce type 1 or type 2 errors.
- **Random (Non Differential Classification) Misclassification** • Random error applied to the measurement of an exposure or outcome. Errors in classification can only produce type 2 errors, except if applied to a confounder or to an exposure gradient.
- **Bias** • Error in design or execution of a study, which produces results that are consistently distorted in one direction because of nonrandom factors. • Bias can produce either a type 1 or a type 2 error, but we usually focus on type 1 errors due to bias.
- **Confounding** • It is defined as one which is associated with both the exposure and the diseases, and is unequally distributed in the study and the control groups Bias can occur in RCTs but tends to be a much greater problem in observational studies.

Properties of measurement

a. Validity
   θThe degree to which a measurement measures what it purports to measure (Last) θ Degree to which the data measure what they were intended to measure – that is, the results of a measurement correspond to the true state of the phenomenon being measured (Fletcher) θAlso known as 'Accuracy'
b. Reliability
   The degree of stability expected when a measurement is repeated under identical conditions; degree to which the results obtained from a measurement procedure can be replicated (Last) θ Extent to which repeated measurements of a stable phenomenon – by

different people and instruments, at different times and places – get similar results (Fletcher) θAlso known as 'Reproduciblity' and 'Precision'

Types of bias

- Selection bias is a distortion in the estimate of association between risk factor and disease that results from how the subjects are selected for the study.
- Information bias is due to systematic measurement error or misclassification of subjects on one or more variables, either risk factor or disease status.
- Confounding -results when the risk factor being studied is so mixed up with other possible risk factors that its single effect is very difficult to distinguish.

28. Explain methods, advantages and disadvantages of cross sectional study.

A cross-sectional study examines the connection between diseases (or other health related state) and other variables of interest as they exist during a defined population at one point in time or over a brief period of your time (e.g. calendar year).

Cross-sectional studies are often thought of as providing a snapshot of the frequency of a disease or other health related characteristics (e.g. exposure variables) during a population at a given point in time. Cross-sectional studies are wont to assess the burden of disease or health needs of a population and are particularly useful in informing the design and allocation of health resources.

Types of cross-sectional study

- **Descriptive cross sectional study:**

A cross-sectional survey could also be purely descriptive and wont to assess the burden of a specific disease during a defined population. for instance a random sample of faculties across London could also be wont to assess the prevalence of asthma among 12-14 year people.

- **Analytical cross sectional study:**

Cross-sectional surveys can also be wont to investigate the association between a putative risk factor and a health outcome. However this sort of study is restricted in its ability to draw valid conclusions on the association between a risk factor and health outcome. during a cross-sectional survey the danger factors and outcome are measured simultaneously, and thus it's going to be difficult to work out whether the exposure proceeded or followed the disease.

Strengths and weaknesses of cross-sectional studies

Strengths:

- Relatively quick and straightforward to conduct (no long periods of follow-up).
- Data on all variables is merely collected once.
- Able to live prevalence for all factors under investigation.
- Multiple outcomes and exposures are often studied.
- The prevalence of disease or other health related characteristics are important publicly health for assessing the burden of disease during a specified population and in planning and allocating health resources.
- Good for descriptive analyses and for generating hypotheses.

Weaknesses:

- Difficult to work out whether the result followed exposure in time or exposure resulted from the result.
- Not suitable for studying rare diseases or diseases with a brief duration.

• As cross-sectional studies measure prevalent instead of incident cases, the info will always reflect determinants of survival also as etiology.
• Unable to live incidence.
• Associations identified could also be difficult to interpret.
• Susceptible to bias thanks to low response and misclassification thanks to recall bias.

29. Explain the significance of relative risk and attributable risk.

ATTRIBUTABLE RISK
• It is additionally called Rate difference or Risk difference.
• Attributable risk is that the "difference in rate of a condition" between an exposed population and an unexposed population.
• Mostly calculated in cohort studies, where individuals are assembled on exposure status & followed over a period of your time .
• Then, the investigators count the occurrence of the disease.
• The cohort is then subdivided by the extent of exposure and therefore the frequency of disease is compared between subgroups.
• One is taken into account exposed & another unexposed.

RELATIVE RISK
• Relative risk is additionally called us risk ratio.
• It is that the ratio of the probability of an occasion occurring (Ex: development of an adverse drug reaction to a drug) in an exposed group to the probability of the event occurring in non-exposed group.

- Relative risk = $\frac{\text{Proportion of events in experimental group}}{\text{Proportion of events in control group}}$

- RR above 1 indicates treatment or exposure is associated with the outcome and below 1, means that the treatment is negatively associated with the outcome.
- When the rate in the exposed group is equal to the rate in the comparison group RR will be equal to 1.
- An RR of 2 means, the rate in the exposed group is twice that of non exposed group.

- An RR of 0.5 means, the rate in the exposed persons is half that of non exposed persons.

Example: The probability of developing allergy among users of perfume was 20% and among those not using perfume 1%

RISK	ALLERGY STATUS	
	Present	Absent
• Perfume users	a	b
• Perfume non-users	c	d

Here, a = 20
b = 80
c = 1
d = 99

Then the relative risk of allergy associated with users of perfume would be:

$$RR = \frac{a/(a+b)}{c/(c+d)}$$

$$RR = \frac{20/100}{1/100}$$

$$RR = 20$$

31. Write a note on case reports with its advantages and disadvantages?

INTRODUCTION:

• Case report is an example of observational descriptive study in Pharmaco-epidemiology.
• It may be a non scientific method , and is one among the only methods in Pharmaco-epidemiology.
• Quite often, experts consider it together of the weakest sort of evidence for causation.
• Case reports are simply reports of events observed in single patients. A case report describes one patient who was exposed to a drug and experiences a specific , usually adverse outcome.
• Case reports are useful for raising hypothesis about drug effects, which should be tested with more rigorous study designs.
• However, during a case report, one cannot know, if the patient reported is either "typically of these with the exposure" or "typically of these with the disease".
• In a case report one cannot usually determine whether the adverse outcome was thanks to the drug exposure or would have would have happened anyway.
• Case reports are hypothesis generating reports. A case report isn't ordinarily wont to make a report (or) statement on causation of an occasion .

Advantages:

• They function an alerting mechanism for clinician's, investigators et al. that a drug (or) group of medicine could produce a given effect.
• It prompts clinicians to remember of the potential problems and to report other such occurrences.
• They may directly cause hypothesis generation which will guide research.
• The most serious adverse drug reactions are detected by a set of single case reports.

Disadvantages:

• Case reports are the weakest sort of evidence for causation. it's very rare that a case report are often wont to make a press release about causation.

32. Write a note on case series with its advantages and disadvantages?

• **Case series**, like case reports are observational descriptive studies in pharmaco-epidemiology. it's a qualitative (descriptive) non-experimental method and is taken into account stronger than Case Reports.
• Case series also are referred to as a Clinical series. it's a gaggle or cluster of case reports generated by single/group of clinicians or hospitals or pharmaceutical companies or regulatory agencies like Food and Drug Administration (FDA) or Drugs Controller.
• It may be a sort of medical research study that tracks subjects with a known exposure, like patients who have received same medicine.
• A set of sequential case reports makes a case series. Case series are collections of patients all of whom have one exposure and whose clinical outcomes are then evaluated and described. The patients are often identified for the case series either supported the exposure or on the result .
• The case series studies are useful in quantifying the incidence of an adverse reaction and arc generally used for the study of newly licensed or marketed medicines.
• The greater the amount of common experiences occurred to patients, the stronger are going to be the signal to support a conclusion. If six patients developed aplastic anaemia after administration of an equivalent medications, which will raise a robust suspicion compared to at least one person developing aplastic anaemia

Advantages:

• Useful for hypothesis generation.
• Informative for very rare disease with few established risk factors.
• Characterizes averages for disorder.

Disadvantages:

• Cannot study cause and effect relationships.
• Cannot assess disease frequency.

Example of the case series study:

During 1950, 8 cases of cancer lung were admitted to different hospitals during an equivalent period of your time . Taking history from these patients showed that they were miners. This unusual circumstance suggested that the miners could also be exposed to something. Investigating this circumstance showed high concentration of radon gas. A hypothesis was formulated that carcinoma is said to exposure to radon.

33. Explain Multi Attribute Utility Theory (MAUT) and System of Objectified Judgement Analysis (SOJA)?

The use of multiattribute utility theory (MAUT) to make a formulary decision involving calcium-channel blockers (CCBs) is described. The MAUT method is a procedure for identifying, characterizing, and comparing the many variables that may affect a decision. Although applications in pharmacy have been infrequent, MAUT should be particularly appealing to formulary committees. The steps of the MAUT method are (1) determine the viewpoint of the decision makers, (2) identify the decision alternatives, (3) identify the attributes to be evaluated, (4) identify the factors to be used in evaluating the attributes, (5) establish a utility scale for scoring each factor, (6) transform the values for each factor to its utility scale, (7) determine weights for each attribute and factor, (8) calculate the total utility score for each decision alternative, (9) determine which decision alternative has the greatest total score, and (10) perform a sensitivity analysis.

A model for drug decision making for formulary purposes is described, the System of Objectified Judgement Analysis (SOJA). In the SOJA method, selection criteria for a given group of drugs are prospectively defined and the extent to which each drug fulfils the requirements for each criterion is determined. Each criterion is given a relative weight, i.e. the more important a given selection criterion is considered, the higher the relative weight. Both the relative scores for each drug per selection criterion and the relative weight of each criterion are determined by a panel of experts in this field. The following selection criteria are applied in all SOJA scores:

clinical efficacy, incidence and severity of adverse effects, dosage frequency, drug interactions, acquisition cost, documentation, pharmacokinetics and pharmaceutical aspects.

34. Explain in detail various costs involved in acquisition of health care facility

Types of Costs

a. Direct costs Medical vs Nonmedical
b. Indirect costs
c. • Intangible costs
d. • Opportunity costs

• Direct Medical Costs:

Costs of medical service These include: • Fixed costs or costs that do not vary immediately with the number of patients treated. E.g. capital costs of hospital building or equipment etc. • Variable costs or costs that vary immediately with number of patients treated. E.g. costs of drugs, syringes, needles etc.

• Direct non-medical costs: • Costs incurred by the patient in receiving medical care. E.g. transportation to and from hospital.

- **Indirect cost:** e.g. income lost because of absenteeism, loss of productivity • Intangible costs • Costs of pain, worry and other suffering which a patient or his family might suffer
- **Opportunity costs:** • The amount lost by not using economic resources in its best alternative use (labour, capital, building, management etc.) • Resources invested in one area will be at expense of loss of another opportunity.

PERSPECTIVES OF PHARMACOECONOMICS

• Patient perspective • Provider perspective • Payer perspective • Societal perspective

PATIENT PERSPECTIVE ¬All the relevant cost and consequences experienced by the patient ¬Included costs: Direct Indirect Intangible

PROVIDER PERSPECTIVE ¬Concerned with the expenses of providing products or services ¬Included costs: -Direct costs only

PAYER PERSPECTIVE ¬Social Security/Government, third party payers eg. private insurance companies and employers ¬Included costs: -Direct costs -Indirect costs relevant to employers lost workdays lost productivity at work

SOCIETAL PERSPECTIVE ¬ The broadest of all perspectives that comprehensively evaluates all costs and consequences ¬ Considers the benefits to society as a whole Included costs: - Direct; overall cost of providing care - Indirect; loss of productivity

35. What are the possible outcomes of a well-defined pharmacoeconomic study and what are the steps involved in planning a pharmacoeconomic study with pharmacoeconomic evaluation?

Pharmacoeconomics refers to the scientific discipline that compares the value of one pharmaceutical drug or drug therapy to another. It is a sub-discipline of health economics. A pharmacoeconomic study evaluates the cost and effects of a pharmaceutical product. There are several types of pharmacoeconomic evaluation: cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis and cost-utility analysis. Pharmacoeconomic studies serve to guide optimal healthcare resource allocation, in a standardized and scientifically grounded manner. One important consideration in a pharmacoeconomic evaluation is to decide the perspective from which the analysis should be conducted.

Pharmacoeconomic research is used **to identify, measure, and compare the costs, risks, and benefits of programs, services, or therapies and determine which alternative produces the best health outcome for the resources invested**.

- **1** Pharmacoeconomics has been defined as the description and analysis of the costs of drug therapy to health care systems and society—it identifies, measures, and compares the costs and consequences of pharmaceutical products and services.
- **2** Pharmacoeconomic studies categorize costs into four types: direct medical, direct nonmedical, indirect, and intangible.

A well-designed pharmacoeconomic analysis involves 10 steps:

(1) defining the problem,

(2) determining the study's perspective,

(3) determining the alternatives and outcomes,

(4) selecting the appropriate pharmacoeconomic method,

(5) placing monetary values on the outcomes,

(6) identifying study resources,

(7) establishing the probabilities of the outcomes,

(8) applying decision analysis,

(9) discounting costs or performing a sensitivity or incremental cost analysis, and

(10) presenting the results, along with any limitations of the study. By adhering to the analytic steps described, the pharmacist undertaking a pharmacoeconomic evaluation has the greatest likelihood of obtaining valid and useful results.

- **3** Perspective is a pharmacoeconomic term that describes whose costs are relevant based on the purpose of the study.
- **4** There are four ways to measure outcomes, and each type of outcome measurement is associated with a different type of pharmacoeconomic analysis: cost-minimization analysis (CMA), cost-benefit analysis (CBA), cost-effectiveness analysis (CEA), and cost-utility analysis (CUA).
- **5** There are two common methods that economists use to estimate a value for health-related consequences, the human capital approach and the willingness-to-pay approach.
- **6** A CUA takes patient preferences, also referred to as utilities, into account when measuring health consequences.
- **7** All four types of analyses described (CMA, CBA, CEA, and CUA) should follow 10 general steps.
- **8** A sensitivity analysis allows one to determine how the results of an analysis would change when these best guesses or assumptions are varied over a relevant range of values.
- **9** Decision analysis is the application of an analytical method for systematically comparing different decision options. Decision analysis graphically displays choices and performs the calculations needed to compare these options.

36. Define drug formulary? Explain various parameters which are analysed in formulary decision making process

A drug formulary is a list of prescription drugs by generic name (often also mentioning brand names) used by medical practitioners to identify drugs that offer greatest value.Formularies are developed by committees consisting of physicians, nurse practitioners, public health experts and pharmacists. They are revised regularly

by the same authorities.Drugs are chosen for the formulary depending on on their effectiveness, safety and appropriateness

The formulary system adds an important component to the DTC and the health care system. A system of evaluating and selecting the most appropriate medicines for the formulary will bring numerous benefits. These include rational use of medicines, improved health care outcomes, improved efficiency in the procurement and inventory management systems, regular supply of essential medicines, and a significant decrease in overall health care cost.

37. What are the general operational principles for conducting an ad-hoc study?

- ☐ The data sources available for pharmacoepidemiological studies as Ad hoc sources are those that are collected during post marketing surveillance studies
- ☐ Ad hoc is concerned mainly with one specific purpose i.e providing data regarding drug safety in long term use or about the drug aspects in a large population which is seen in post marketing studies compared to pre marketing studies.

DIFFERENT KINDS OF DATA SOURCES:

- ☐ 1. Spontaneous reporting
- ☐ 2. Global drug Surveillance
- ☐ 3. Case-Control Surveillance
- ☐ 4. Prescription-Event Monitoring

1. Spontaneous reporting of adverse events:

• Spontaneous reporting systems are the foremost common method utilized in Pharmacovigilance to get signals on new or rare adverse events, which isn't discovered during clinical trials.
• Very useful in generating hypothesis, and to seek out out possible explanations for the adverse event in question.
• In order to make sure that safe and effective pharmaceuticals are available, FDA relies on:

1. Voluntary reporting by health care professionals or consumers.
2. Mandatory reporting of Adverse Events by manufacturers as needed by law and regulation.

2. Global Drug Surveillance:

• Global reporting of concerns about suspected adverse drug reactions may be a vital alerting tool.
• The WHO Collaborating Centre for International Drug Monitoring in Uppsala (now referred to as the Uppsala Monitoring Centre, UMC).
• Today, 73 countries — Full official members, 12 countries — associate members
• National centers should report monthly frequency.
• Recently, there has been a world effort to:

1. Harmonize the terms wont to describe the adverse events.
2. To set criteria and definitions for a minimum of the main serious sorts of reactions.
3. To harmonize the way data are stored and communicated internationally.
4. Main agencies involved during this are WHO, CIOMS, ICH and therefore the EU.

CASE-CONTROL SURVEILLANCE

There is no assurance that medications are safe at the time they are released to the market, because premarketing trials for safety and efficacy are

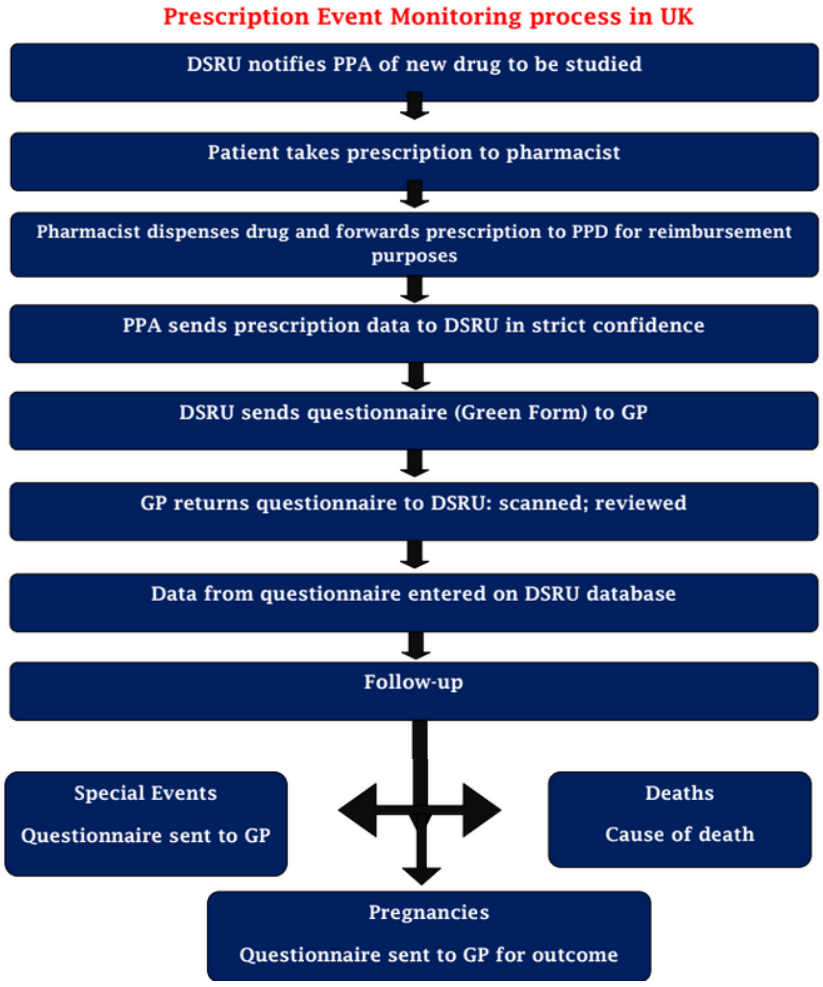
- too small to detect any but common adverse effects and
- too brief to detect effects that occur after long latent intervals or durations of use.
- Postmarketing surveillance serves not only to document unintended adverse effects of medications, but also to document beneficial effects unrelated to the indications for use.

Need for CCS

- Current surveillance systems focus on prescription drugs
- More drugs now are being converted to non-prescription (OTC) medication:
  - Ibuprofen, naproxen, cimetidine
- Large increase in their use due to this conversion
- Initially only for acute/ self-limiting diseases
- Drugs for hypercholesterolemia, osteoporosis, HTN also under consideration
- Increase in use of dietary supplements and herbal supplements

4. Prescription Event Monitoring:

- PEM is a pharmacoepidemiological study in which a cohort of users of a medicine is defined from prescriptions and followed-up for a defined period (often 6-12months) so as to identify all adverse events occurring in the early post-treatment period.
- The limited contribution of spontaneous ADR reporting system in detecting hazards such as oculomucocutaneous syndrome with *Practolol*, led Inman to establish the system of PEM at the Drug Safety Research Unit (DSRU) at Southampton in 1981.
- It is one form of Pharmacovigilance and is complementary to spontaneous reporting of suspected ADRs.
- Method of both hypothesis generation and testing.



39. Define pharma coepidemology and explain the difference between PE and CP?

Pharmacoepidemiology is the study of the use and effects of drugs in large numbers of people.[1(p3)] It is a growing discipline that applies epidemiological techniques to study drug use in a large population.

Pharmacoepidemiology is a branch of science that investigates the use and effects (beneficial and deleterious) of medications ("pharmaco") in large populations ("epidemiology"). Pharmacoepidemiology is called a bridge science bringing together pharmacology and pharmacy, clinical specialties, epidemiology, biostatistics, demography and social sciences. Epidemiology and clinical pharmacology are the two main bridgeheads.

Pharmacoepidemiology versus Clinical Pharmacology

Pharmacology is the branch of medicine and biology concerned with the study of drug action . Clinical Pharmacology is the study of the effects of drugs in humans. Pharmacoepidemiology is a part of Clinical Pharmacology and can provide vital information about the positive and negative effects of any drug, resulting in a better evaluation of the risk/ benefit ratio for the use of a drug in a patient.

Clinical pharmacology is categorized into two main areas: Pharmacokinetics and Pharmacodynamics. Pharmacokinetics (PK) (pharmakon: "drug" and kinetikos: "to do with motion") is dedicated to the determination of the fate of substances administered externally to a living organism. It deals with drug absorption, distribution, metabolism and excretion. Pharmacokinetics is often studied in relation to pharmacodynamics. Pharmacodynamics is the study of the relationship between drug level and drug effect.

Pharmacokinetics may be simply defined as what the body does to the drug, as opposed to pharmacodynamics which may be defined as what the drug does to the body.

Pharmacodynamics and pharmacokinetics make it possible to know the effect of certain drug inside the body of a patient. Pharmacoepidemiology includes contributions from both these fields, exploring the effects achieved by administering a drug regimen.

Pharmacology versus Epidemiology

Epidemiology is the study of the distribution and patterns of health events, health characteristics and their causes or influences in welldefined populations. It is the cornerstone method of public health research, and helps inform policy decisions and evidence-based medicine by identifying risk factors for disease and targets for preventive medicine. Pharmacoepidemilogy is a part of epidemiology since it deals with the effects of drugs in large numbers of people or in a population. Despite the fact that pharmacoepidemilogical approaches can be useful in performing the clinical trials of drugs that are performed before marketing, the major application of these principles is after drug marketing. Pharmacoepidemilogy acquires its focus of inquiry from clinical pharmacology and its methods of inquiry from epidemiology . During this process, various logistical approaches have been developed and methodologic issues have arisen

40. Explain the potential contributions of PE?

 Potential contributions of PEp ¬ (B) New types of information not available from premarketing studies (1) Discovery of previously undetected adverse and beneficial effects (a) Uncommon effects (e.g.: agranulocytosis) (b) Delayed effects (e.g.: DES) (2) Patterns of drug utilization (3) The effects of drug overdoses (4) The economic implications of drug use

 Potential contributions of PEp ¬ (C) General contributions of pharmacoepidemiology (1) Reassurances about drug safety (2) Fulfillment of ethical and legal obligations

 7. Questions that can be answered by PEp ¬ Patterns of use ¬ What are patterns of drug utilization ¬ How are drug utilized in special population ¬ How long do people take this drug e.g.: doxycycline ¬ Safety ¬ What is the frequency of drug induced outcomes ¬ Are there drug drug interactions?

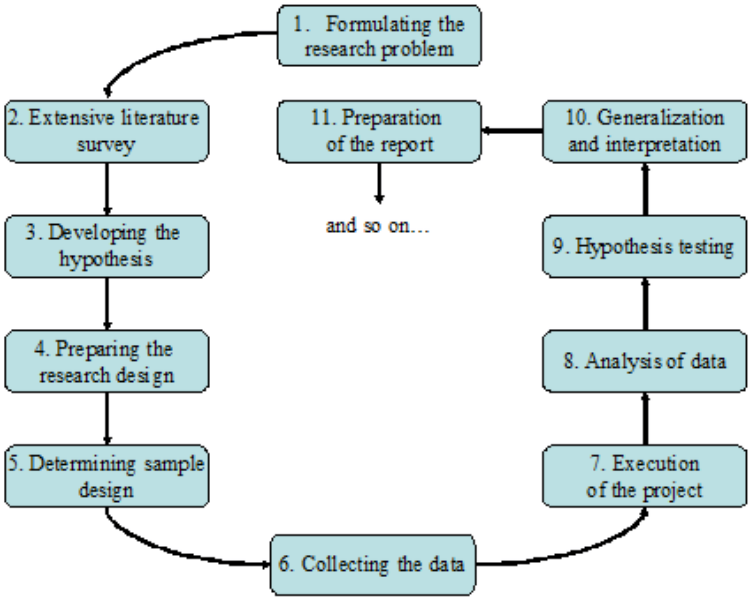
 . ¬ Effectiveness ¬ What are the clinical benefits of this drug ¬ Is drug A more effective than drug B? – Economic evaluation ¬ What are the economic consequences of therapy

41. Explain the overview of scientific method to investigate a research question along with three stage process?

Scientific method, mathematical and experimental technique employed in the sciences. More specifically, it is the technique used in the construction and testing of a scientific hypothesis.

The process of observing, asking questions, and seeking answers through tests and experiments is not unique to any one field of science. In fact, the scientific method is applied broadly in science, across many different fields.

Typically, the scientific method starts with these steps—1) ask a question, 2) research existing sources, and 3) formulate a hypothesis.



43. Explain the approaches to controlling confounding variables?

There are several methods you can use to decrease the impact of confounding variables on your research: **restriction, matching, statistical control and randomization**. In restriction, you restrict your sample by only including certain subjects that have the same values of potential confounding variable

Restriction

In this method, you restrict your treatment group by only including subjects with the same values of potential confounding factors.

Since these values do not differ among the subjects of your study, they cannot correlate with your independent variable and thus cannot confound the cause-and-effect relationship you are studying.

Matching

In this method, you select a comparison group that matches with the treatment group. Each member of the comparison group should have a counterpart in the treatment group with the same values of potential confounders, but different independent variable values.

This allows you to eliminate the possibility that differences in confounding variables cause the variation in outcomes between the treatment and comparison group. If you have accounted for any potential confounders, you can thus conclude that the difference in the independent variable must be the cause of the variation in the dependent variable.

Statistical control

If you have already collected the data, you can include the possible confounders as control variables in your regression models; in this way, you will control for the impact of the confounding variable.

Any effect that the potential confounding variable has on the dependent variable will show up in the results of the regression and allow you to separate the impact of the independent variable.

Randomization

Another way to minimize the impact of confounding variables is to randomize the values of your independent variable. For instance, if some of your participants are assigned to a treatment group while others are in a control group, you can randomly assign participants to each group.

Randomization ensures that with a sufficiently large sample, all potential confounding variables—even those you cannot directly observe in your study—will have the same average value between different groups. Since these variables do not differ by group assignment, they cannot correlate with your independent variable and thus cannot confound your study.

44. Explain the criteria for causal nature of an association?

Association may be defined as the concurrence of two variables more often than would be expected by chance. Epidemiological studies determine various associations between an exposure and a disease. Further, its important to find out whether the exposure is causal for the disease or not.

 Criteria for Causal Association Bradford Hill's criteria for making causal inferences-

1.Strength of association

2.Dose-Response relationship

3.Lack of temporal ambiguity

4.Consistency of findings

5.Biologic plausibility

6.Coherence of evidence

7.Specificity of association

 1.Strength of association • Measured by the relative risk (or odds ratio). • The stronger the association, the more likely it is that the relation is causal. • Relative risk is the ratio of the incidence of the disease among exposed and the incidence among non-exposed.

 Example- Risk for development lung cancer 8.6 times higher in smokers than in non-smokers.

 2.Dose-Response relationship • As the dose of exposure increases, the risk of disease also increases • If present, it is strong evidence for a causal relationship. • Absence of a dose-response relationship does not necessarily rule out a causal relationship. • In some cases in which a threshold may exist, no disease may develop up to a certain level.

3.Lack of temporal ambiguity • Exposure to the factor must have occurred before the disease developed • The temporal relationship is important in regard to the length of the interval between exposure and disease • It's easier to establish a temporal relationship in a prospective cohort study than in a case-control study or a retrospective cohort study.

 Example- Consumption of contaminated food should precede the symptoms of food poisoning.

 4.Consistency of findings • The relationship should be found consistently in different studies and in different populations. • Unless there is a clear reason to expect different results, replication of the findings should be there.

 5.Biologic plausibility • Biologic plausibility refers to coherence with the current body of biologic knowledge • Epidemiologic findings should be consistent with existing biologic knowledge. • Example- Carcinogens from cigarette smoke deposits in the lung over a period of time leading to lung cancer.

 6.Coherence of evidence • If a relationship is causal, we would expect the findings to be consistent with other data. • For the appraisal of causal significance of an association it should be coherent with known facts that are thought to be relevant.

 Example- Peptic ulcer disease • Prevalence of H.pylori is same in men as in women. Incidence of duodenal ulcer in both have been proved to be equal in recent years. • Prevalence of peptic ulcer disease is believed to have peaked in the latter part of 19th century cause of poor living standards.

 7.Specificity of association • Association is specific when a certain exposure is associated with only one disease • When specificity of an association is found, it provides additional support for a causal inference • Absence of specificity in no way negates a causal relationship.

 Example- Prevalence of H.pylori in patients with duodenal ulcer is 90% to 100%. However, it is found even in some patients of gastric ulcer and even in asymptomatic individuals.

45. Give the advantages and disadvantages of epidemiologic study designs?

Advantages and disadvantages of cohort study

Advantages

- Incidence can be directly calculated
- Direct estimation of the relative risk (RR)
- More than one outcome of the risk factor can be studied
- Dose response relationship with exposure can be studied
- Temporal association of the exposure with the outcome can be seen
- Certain biases like recall bias, interviewer's bias are not a problem

Disadvantages

- The major disadvantage is the huge requirement for resources, viz. time, money and personnel
- Unsuitable for rare diseases
- Long periods of follow up needed
- Attrition is a problem as long follow up is required
- Ethical problems are more because as evidence of the RF accumulates, it becomes the duty of the investigator to educate those with the risk factor. Wait and watch may be unethical
- Only one or a few risk factors can be studied.

Strengths and weaknesses of cross-sectional studies

Strengths

- Relatively quick, cheap and easy to conduct (no long periods of follow-up).
- Data on all variables is only collected once.
- Able to measure prevalence for all factors under investigation.
- Multiple outcomes and exposures can be studied.

- The prevalence of disease or other health-related characteristics are important in public health for assessing the burden of disease in a specified population and in planning and allocating health resources.
- Good for descriptive analyses and for generating hypotheses.

Weaknesses

- Difficult to determine whether the exposure or outcome came first (there may be reverse causality – see chapter 12 "*Association and Causation*")
- Not suitable for studying rare diseases or diseases with a short duration.
- As cross-sectional studies measure prevalent rather than incident cases, the data will always reflect determinants of survival as well as aetiology.[1]
- Unable to measure incidence.
- Associations identified may be difficult to interpret.
- Susceptible to biases such as responder bias, recall bias, interviewer bias and social acceptability bias

Strengths and weaknesses of case-control studies

Strengths

- Cost-effective relative to other analytical studies such as cohort studies.
- Case-control studies are retrospective, cases are identified at the beginning of the study therefore there is no long follow-up period (compared to cohort studies).
- Efficient for the study of diseases with long latency periods.
- Efficient for the study of rare diseases.
- Good for examining multiple exposures simultaneously.

Weaknesses

- Particularly prone to bias; especially selection, recall and observer bias.
- Case-control studies are limited to examining one outcome.
- Unable to estimate incidence rates of disease (unless study is population based).
- Poor choice for the study of rare exposures.
- The temporal sequence between exposure and disease may be difficult to determine.

49. What is analysis of secular trends on ecological studies?

- The secular trend describes the occurrence of disease over a prolonged period, usually years; it is influenced by the degree of immunity in the population and possibly nonspecific measures such as improved socioeconomic and nutritional levels among the population
- Many diseases show remarkable fluctuations in incidence over time. Rates of acute infection can vary appreciably over a few days, but epidemics of chronic disorders such as lung cancer and coronary heart disease evolve over decades.
- If time or secular trends in disease incidence correlate with changes in a community's environment or way of life then the trends may provide important clues to aetiology. Thus, the currently increasing incidence of melanoma in Britain has been linked with greater exposure to sunlight and successive rises and falls in mortality from cervical cancer have been related to varying levels of sexual promiscuity, as evidenced by notification rates for gonorrhoea.
- Like geographical studies, analysis of secular trends may be biased by differences in the ascertainment of disease. As health services have improved, diagnostic criteria and techniques have changed.

- Furthermore, whereas in geographical studies the differences are accessible to current inquiry, validating secular changes is more difficult as it depends on observations made and often scantily recorded many years ago. Nevertheless, the reality – if not the true size – of secular trends can often be established with reasonable certainty. The rise and subsequent fall in the incidence of appendicitis in Britain during the past 100 years is a good example.

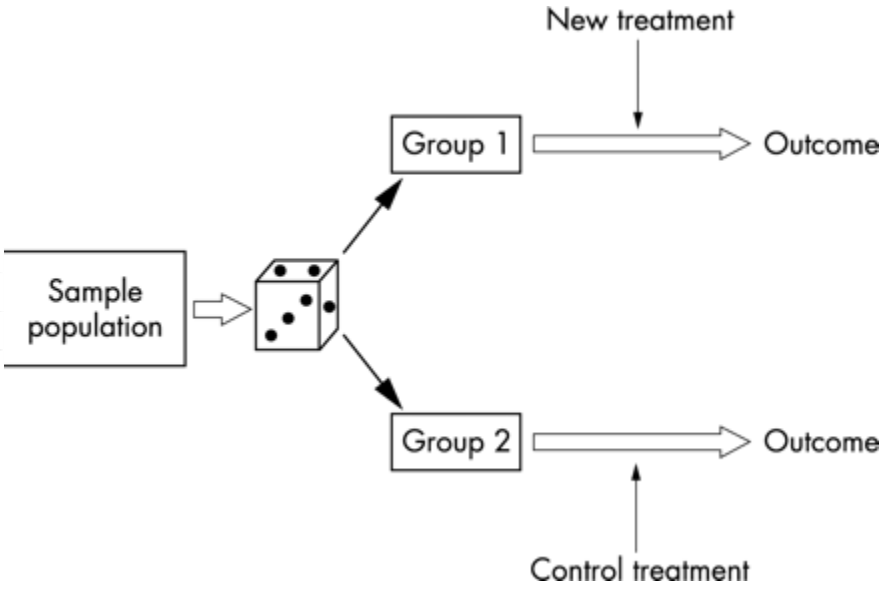
51. Compare between case control and cohort studies?

Comparison of Case Control and Cohort Studies

- Both Case Control and Cohort Studies are powerful analytical tools for testing Hypothesis in pharmacoepidemiology.
- The choice between them depends on the inquiries to be answered.
- Case Control studies are less costly compared to Cohorts.
- In case control only the relative risk are often directly estimated with the assistance of odds ratio.
- In the case of Cohorts incidence rates can directly calculated and both relative and attributable risks are often determined.
- Cohort Studies often need large or huge number of patients while only a sample of the source population is required just in case Control.
- Case control can give information on one or limited number of outcomes while Cohorts give information on variety of various outcomes.

52. Explain randomised clinical trial?

The randomised control trial (RCT) is a trial in which subjects are randomly assigned to one of two groups: one (the experimental group) receiving the intervention that is being tested, and the other (the comparison group or control) receiving an alternative (conventional) treatment (fig 1). The two groups are then followed up to see if there are any differences between them in outcome. The results and subsequent analysis of the trial are used to assess the effectiveness of the intervention, which is the extent to which a treatment, procedure, or service does patients more good than harm. RCTs are the most stringent way of determining whether a cause-effect relation exists between the intervention and the outcome.



53. Enlist the national and international post marketing safety databases?

- Adverse Event Reporting Databases at the Food and Drug Administration (FDA): FAERS and VAERS
- Adverse Event Reporting Databases at the European Medicines Agency (EMA): EudraVigilance and VAESCO
- WHO safety database (VigiBase)

India has developed adr pvpi android app for better submission of adr, thus improving the volunteer reporting of adrs.
Or http://www.ipc.gov.in submit a adrs report on the web portal.

54. What are reporting ratios?

The proportional reporting ratio (PRR) is the proportion of spontaneous reports for a given drug that are linked to a specific adverse outcome, divided by the corresponding proportion for all or several other drugs.

The proportional reporting ratio is a statistic that is used to summarize the extent to which a particular adverse event is reported for individuals taking a specific drug, compared to the frequency at which the same adverse event is reported for patients taking some other drug.

55. Explain signal detection and approach for detecting signals from a post marketing safety database?

Signal detection in Pharmacovigilance involves looking at the adverse reaction data for patterns that suggest new safety information and specifically whether the new information changes the benefit to risk ratio associated with the use of a pharmaceutical product.

The process of signal management in pharmacovigilance is a set of activities, which aim to determine whether there are new risks associated with a particular drug, or whether known risks associated with a particular drug have changed.

Sources for the detection of signals:

- Spontaneous reporting
- Active monitoring systems
- Interventional studies (clinical trials)
- Non-interventional studies (pharmacoepidemiology studies)
- Non-clinical studies (e.g. animal toxicology studies)
- Systematic reviews (i.e. thorough review of the published literature)
- Meta-analyses (i.e. mathematical pooling of all the clinical trial data)

Signals arising from spontaneous reports may also be evaluated via:

- Monitoring large adverse drug reaction databases such as EudraVigilance and the FDA AERs system
- Published articles
- Periodic Safety Update Reports (PSURs)

Ongoing Benefit-Risk Monitoring

The process for managing signals must systematically address the following:

- Signal detection
- Validation and Confirmation
- Analysis
- Prioritization
- Assessment
- Recommendation(s) for action

56. Explain about national pharmacovigilance system?

CDSCO Directorate General of Health Services, under the help of "Ministry of Health and Family Welfare", Government of India together with "Indian Pharmacopoeia commission, Ghaziabad (U.P) has started Pharmacovigilance program for shielding the health of the patients by assessing drug safety in India.

• Indian pharmacopoeia commission (IPC), Ghaziabad is functioning as a National Coordinating centre (NCC) for Pharmacovigilance Program of India (PVPI).

• 150 ADR Monitoring centers, were established in various medical institutions or hospitals across India to watch and collect ADR reports under NCC-PVPI.

What to report:

• PVPI encourages all kinds of suspected adverse drug reactions reporting, whether or not they are known, unknown, serious or non serious, etc.

• Adverse drug reactions related with the utilization of allopathic medicines, vaccines, traditional medicines, medical devices, contrast media, etc. are often reported.

Where to report:

• All health care professionals (clinicians, dentists, pharmacists, nurses) and patients or Consumers can report ADR's to NCC or AMCs.

• The pharmaceutical companies also can send individual case safety reports for his or her product to NCC.

How to report:

• Suspected ADR reporting forms for healthcare professionals and consumers are available on the web site of IPC to report ADR.

• To remove barrier in ADR reporting, the buyer reporting form are made available in 10 vernacular languages (Hindi, Tamil, Telugu, Kannada, Bengali Gujarati, Assamese, Marathi, Oriya and Malayalam).

57. Explain the strengths and limitations of post marketing safety reporting system?

Spontaneous reporting of adverse drug reactions continues to be the principal method used for monitoring the safety of marketed drugs. Despite the many successes attributed to these schemes, they can reliably detect only a small fraction of the range of possible drug-related events and provide virtually no useful quantitative data

Spontaneous monitoring should be supplemented by the systematic monitoring of cohorts of users of new drugs, using record-linkage to track their subsequent health.

58. Define data mining?

Data mining **recognizes an alert from any available source data from pre- or post-marketing studies**, although in practice data from postmarketing safety databases are largely used.

Data mining encompasses a number of statistical techniques including **cluster analysis, link analysis, deviation detection and disproportionality assessment** which can be utilized to determine the presence of and to assess the strength of ADE signals.

59. Explain about the claims and other administrative database?

Administrative databases are **massive repositories of data collected in healthcare for various purposes**. Such databases are mainly maintained in hospitals, health maintenance organisations and health insurance organisations.

Claims data, also known as administrative data, are another sort of electronic record, but on a much bigger scale. Claims databases collect information on millions of doctors' appointments, bills, insurance information, and other patient-provider communications.

The good thing about claims data is that, like other medical records, they come directly from notes made by the health care provider, and the information is recorded at the time patient sees the doctor. Also, because of the large sample size of claims data, researchers can analyze groups of patients with rare illnesses and medical conditions. The downside to using claims data is there may be low validity due to certain illegal billing practices, like ordering unnecessary tests or billing for services that were not provided.

The three major administrative databases maintained by the federal government are the CMS-64 Quarterly Expense Report to the Centers for Medicare & Medicaid Services (CMS), the Medicaid Statistical Information System (MSIS), and the Children's Health Insurance Program (CHIP) Statistical Enrollment Data System (SEDS).

The purpose of the Medcaid Statistical Information System (MSIS) is to collect, manage, analyze, and disseminate information on eligibles, beneficiaries, utilization, and payment for services covered by state Medicaid programs (see www.cms.gov/MSIS [September 2010]). The MSIS data serve multiple purposes, including health care research and evaluation activities, program utilization and expenditures forecasting, analyses of policy alternatives, responses to congressional inquiries, and matches to other health-related databases. States provide CMS with quarterly computer files containing, among other data items, specified data elements for persons covered by Medicaid (eligible files).

ength	Medicaid Statistical Information System (MSIS)	weaknes
	• Granular data, supporting a wide range of spending and enrollment analyses • Has improved markedly over the years, both in terms of timeliness and data quality	• Size and complexity make it susceptible to submission delays, although much improvement has been made (2008 nearly complete) • Its very size and complexity can contribute to missing data and a wide range of anomalies • Managed care spending not separated into services
	Statistical Enrollment Data System	
	• Available earlier than MSIS	• Collects only aggregate enrollment data

60. What are the strengths and weakness of computerised database?

Advantages

- Reduced data redundancy
- Reduced updating errors and increased consistency
- Greater data integrity and independence from applications programs
- Improved data access to users through use of host and query languages
- Improved data security
- Reduced data entry, storage, and retrieval costs
- Facilitated development of new applications program

Disadvantages

- Database systems are complex, difficult, and time-consuming to design
- Substantial hardware and software start-up costs
- Damage to database affects virtually all applications programs
- Extensive conversion costs in moving form a file-based system to a database system
- Initial training required for all programmers and users

61. What are MRDBs?

Medical record database or patient record database may **contain data collected over long periods of time**, sometimes for a patient's life-time. They are accessed by a variety of users for different patient-care purposes, to satisfy legal requirements and assist with administrative issues, such as reimbursement. MRDBs are used to collect data of patient right from his/her first admission to a hospital. Any clinic visits are also to be entered into these records. This helps in assessings the risk factors or other causes of diseases/ disorder that the patient might be encountering.

62. What are electronic medical records (EMRs)?

Electronic medical records (EMRs) are **digital versions of the paper charts in clinician offices, clinics, and hospitals**. EMRs contain notes and information collected by and for the clinicians in that office, clinic, or hospital and are mostly used by providers for diagnosis and treatment.

The EMR or electronic medical record refers to everything you'd find in a paper chart, such as medical history, diagnoses, medications, immunization dates, allergies. While EMRs work well within a practice, they're limited because they don't easily travel outside the practice. In fact, the patient's medical record might even have to be printed out and mailed for another provider to see it.

The top list of EMR consist of the following

- **CureMD**
- **athenaOne**
- **epic care**
- **AdvancedMD**
- **Cerner power chart**

63. Discuss the health maintenance organisations/ health plans?

- A health maintenance organization (HMO) is a network or organization that provides health insurance coverage for a monthly or annual fee.
- An HMO is made up of a group of medical insurance providers that limit coverage to medical care provided through doctors and other providers who are under contract with the HMO.
- These contracts allow for premiums to be lower—since the healthcare providers have the advantage of having patients directed to them—but they also add additional restrictions to HMO members.
- HMO plans require that participants first receive medical care services from an assigned provider known as the primary care physician (PCP).

- Preferred provider organizations (PPOs) and point-of-service plans (POS) are two types of healthcare plans that are alternatives to HMOs.

Health maintenance organizations (HMOs) provide health insurance coverage for a monthly or annual fee. An HMO limits member coverage to medical care provided through a network of doctors and other healthcare providers who are under contract with the HMO.1 These contracts allow for premiums to be lower than for traditional health insurance—since the health providers have the advantage of having patients directed to them. They also add additional restrictions to the HMO's members

An HMO is an organized public or private entity that provides basic and supplemental health services to its subscribers. The organization secures its network of health providers by entering into contracts with primary care physicians, clinical facilities, and specialists. The medical entities that enter into contracts with the HMO are paid an agreed-upon fee to offer a range of services to the HMO's subscribers. The agreed payment allows an HMO to offer lower premiums than other types of health insurance plans while retaining a high quality of care from its network.

64. Enlist the current and past multisite multiproject research programs within HMORN?

The HMO Research Network (HMORN) Virtual Data Warehouse (VDW) is a public, non-proprietary, research-focused data model implemented at 17 health care systems across the United States. The HMORN has

created a governance structure and specified policies concerning the VDW's content, development, implementation, and quality assurance.

Unfortunately, even the largest health-plan data warehouses are often insufficient to address many research questions. To address this limitation, multicenter collaborations are formed to aggregate data across institutions to obtain larger and more representative populations. Consortia such as the Centers for Disease Control and Prevention's (CDC) Vaccine Safety Datalink (VSD), the Agency for Healthcare Research and Quality (AHRQ) Centers for Education and Research on Therapeutics (CERT), the National Heart Lung and Blood Institute's (NHLBI) Cardiovascular Research Network, and the National Cancer Institute (NCI) Cancer Research Network (CRN) have designed data models, infrastructure, and governance that allow data aggregation across institutions for research purposes while ensuring that health care organizations maintain local control over their highly regulated and proprietary data

65. Explain about Cancer research network (CRN), Cardiovascular research network (CVRN), Vaccine safety database (VSD)? Explain the data structure of Medicaid database?

The Cancer Research Network (CRN) is an NCI-funded initiative to support and facilitate cancer research based in non-profit integrated health care delivery settings. The CRN welcomes collaborations that result in research projects that improve knowledge about cancer etiology, prevention, early detection, treatment and prognosis, and that decreases the burden of cancer across the cancer care spectrum. The integrated health care settings provide unique advantages for conducting population sciences research. Through the links below, find out more about the CRN, its activities, and how to develop collaborations with the CRN's many investigators with expertise in conducting public-domain cancer research in these settings.

The Vaccine Safety Datalink (VSD) is a collaborative project between CDC's Immunization Safety Office and nine health care organizations. The VSD started in 1990 and continues today in order to monitor safety of vaccines and conduct studies about rare and serious adverse events following immunization.

The VSD uses electronic health data from each participating site. This includes information on vaccines: the kind of vaccine given to each patient, date of vaccination, and other vaccinations given on the same day. The VSD also uses information on medical illnesses that have been diagnosed at doctors' offices, urgent care visits, emergency department visits, and hospital stays. The VSD conducts vaccine safety studies based on questions or concerns raised from the medical literature and reports to the Vaccine Adverse Event Reporting System (VAERS). When there are new vaccines that have been recommended for use in the United States or if there are changes in how a vaccine is recommended, the VSD will monitor the safety of these vaccines.

The Cardiovascular Research Network represents a new paradigm in the approach to cardiovascular quality of care and outcomes research among community-based populations. Its unique ability to characterize longitudinally large, diverse populations will yield novel insights into contemporary disease and risk factor surveillance, management, outcomes, and costs. The Cardiovascular Research Network aims to become the national research partner of choice for efforts to improve the prevention, diagnosis, treatment, and outcomes of cardiovascular diseases.

Cardiovascular research network sites bring complementary content and methodological expertise and a diverse population of ≈11 million individuals treated through various health care delivery models. Each site's rich electronic databases (eg, sociodemographic characteristics, inpatient and outpatient diagnoses and procedures, pharmacy, laboratory, and cost data) are being mapped to create a standardized virtual data warehouse to facilitate rapid and efficient large-scale research studies. Initial projects focus on (1) hypertension recognition

and management, (2) quality and outcomes of warfarin therapy, and (3) use, outcomes, and costs of implantable cardioverter defibrillators.

Medicaid Analytic eXtract (MAX) data are a set of de-identified person-level data files with information on Medicaid eligibility, service utilization, diagnoses, and payments. Derived from the Medicaid Statistical Information System (MSIS), the Medicaid MAX data contain one person summary (PS) file and four claims files. Claims files include Inpatient (IP), Long Long-Term Care (LTC), Other Services (OT), and Prescription Drug (RX). These claims data include fee for service (FFS) claims as well as managed care encounter and premium payments. Owned by the Centers for Medicare and Medicaid (CMS), Medicaid data cover everyone enrolled in Medicaid and Children's Health Insurance Program (CHIP)S

66. What are the strengths and weakness of Medicaid, Medicare, and department of Veterans Affairs?

Advantages of Medicaid

1 Medicaid is a program that focuses on both elderly individuals and individuals who suffer from various disabilities. More specifically, seniors and disabled individuals have been shown to account for approximately two-thirds of medical aid spending in the United States.

1 Those who are on Medicaid will find that their patient copay costs are generally lower and much more affordable.

Disadvantages of Medicaid

5 While Medicaid is, as previously mentioned, designed to serve lower-income individuals, not all low-income individuals will actually qualify for this service. Each state has its own set of specific guidelines in terms of qualifying for Medicaid.

6 In the event that someone on Medicaid ends up suffering an emergency, they can sometimes end up enduring lower quality treatment simply because they are on Medicaid. On Medicaid, the affected individual may not be able to undergo some of the necessary treatment.

Medicare is wonderful. Medicare's fee structure, low co-pay, easy administration, wide acceptance, broad coverage and low restrictions make it most useful

Patients and medical professionals can and do abuse the system. LIMITED CLINICAL information. It does not have pharmacy benefit for outpatient medications thus the benefits cannot be studied.

The VA, through its Veterans Benefits Administration (VBA), provides a variety of services for veterans including **disability compensation, pension, education, home loans, life insurance, vocational, rehabilitation, survivors' benefits, health care, and burial benefits**.

4 challenges are:

(1) long- standing performance problems, (2) claims-processing complexities, **(3) challenges to improving performance**, and (4) VBA's initiatives to improve performance.

67. Explain the prescription drug database in Canadian provincial database

In Canada, databases have been created for the administration of the universal health-care program, which covers outpatient and inpatient services. Public prescription drug programs are also available, but the characteristics of the programs and the populations covered differ extensively across provinces. The health services and drug programs are under provincial jurisdiction, which results in a fragmentation of the administrative databases by province. For the majority of the Canadian provinces, database linkage has led to the accumulation of population-based longitudinal data on prescriptions and medical services provided to the program members. Some databases have been used widely for pharmacoepidemiologic research (Saskatchewan, Quebec, Ontario, British Columbia, Manitoba). Although the data elements found in databases are fairly homogeneous across provinces, the populations covered, linkage capacities with other data sources, as well as access policy, differ greatly.

Strengths

Canadian databases have been widely used for pharmacoepidemiologic research. Although most studies found in the literature involve a limited number of databases, such as those from Saskatchewan, Ontario, Quebec, British Columbia, and Manitoba, as research capacity within Canada is expanding, one can foresee greater use of the other databases as well. Among the unique features of the Canadian databases are the availability of longitudinal population -based data on prescription drugs and health -care use, and most importantly linkage capacities with other sources of data, such as registries or surveys.

Weaknesses

The technical advantages of the Canadian databases are somewhat offset by decentralization and the access restrictions described above. Although efforts to pool databases are currently ongoing in a number of countries, few attempts have been made in Canada to date. The diffi culty in accessing patient health records through nominal information, for diagnostic validation or to control for unmeasured confounders, is a threat to the validity of studies that aim at assessing the safety or effectiveness of a drug.

The future

Medical services, hospitalizations, and prescription drug databases are widely available in Canada. At present, their potential for use in pharmacoepidemiologic research is somewhat hampered by access restriction and/or delays. Great potential exist for linkage with complementary sources of information such as registries. However, such registries are often local initiatives, with no information centralized in a common repository. Greater linkage capacities between databases and other complementary data sources would be valuable to augment the data sources in Canada, such as laboratory test results. At the present time, the Manitoba bone mass registry is the only provincial source of data on diagnostic test results. The fragmentation of databases across provinces and heterogeneity in custodians leads to a taxonomy of databases that is very complex. In the future, database access and linkage capacities will need to be better communicated in order to implement collaborative projects across provinces.

68. Explain record linkage, patient router files in pharmacy based medical record linkage system?

• Record linkage is that the process of bringing together two or more records concerning an equivalent individual (person), family or entity (e.g. event, object, geography, business etc.).

• To find syntactically distinct data entries that ask an equivalent entity in two or more input files.
• Part of the info cleaning process, which may be a crucial initiative within the knowledge discovery process.

DETERMINISTIC RECORD LINKAGE:

• A pair of records is claimed to be a link if the 2 records agree exactly on each element within a set of identifiers called the match key.
• ALL or NONE
• For example, when comparing two records on surname , street name, year of birth, and street number, and therefore the pair of records is deemed to be a link as long as the names agree on all characters, the years of birth are an equivalent , and therefore the street numbers are identical

pharmacy-based medical record linkage systems have at least three types of fi les in common: a patient router fi le containing the characteristics of patients in the catchment population; a pharmacy - based drug exposure registry; and one or more linked clinical registries obtained from other organizations or health professionals. The exposure and clinical registries are linked to the patient router fi le using a variety of record linkage methods.

A patient router file, in which all patients have a unique identification number, represents essentially all inhabitants of a population in a defined geographic area, such as a region or country. Patient router fi les typically include a unique personal identifier, year of birth, gender, and place of residence, and serve as a router pointing to the fi les where exposure and clinical histories are stored. Patients may enter the population by birth or immigration, and may depart from the population through death or emigration.

70. What are the essential steps to be taken prior to selection of a design for in ad-hoc studies?

71. Explain protocol development in ad-hoc studies?

General Information

- Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).
- Name and address of the sponsor and monitor (if other than the sponsor).
- Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor
- Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.
- Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).
- Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).
- Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

Background Information

- Name and description of the investigational product(s).
- A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

- Summary of the known and potential risks and benefits, if any, to human subjects.
- Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).
- A statement that the trial will be conducted in compliance with the protocol, GCP, and the applicable regulatory requirement(s).
- Description of the population to be studied.
- References to literature and data that are relevant to the trial and that provide background for the trial.

Trial Objectives and Purpose: A detailed description of the objectives and the purpose of the trial.

Trial Design: The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design should include:

- A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.
- A description of the type/design of trial to be conducted (e.g., double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures, and stages.
- A description of the measures taken to minimize/avoid bias, including: (a) Randomization and (b) Blinding.
- A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).
- The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.
- A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial, and entire trial.
- Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.
- Maintenance of trial treatment randomization codes and procedures for breaking codes.
- The identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data.

Selection and Withdrawal of Subjects

- Subject inclusion criteria.
- Subject exclusion criteria.
- Subject withdrawal criteria (i.e., terminating investigational product treatment/trial treatment) and procedures specifying:

(a) When and how to withdraw subjects from the trial/investigational product treatment

(b) The type and timing of the data to be collected for withdrawn subjects

(c) Whether and how subjects are to be replaced

(d) The follow-up for subjects withdrawn from investigational product treatment/trial treatment.

Treatment of Subjects:

- The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.
- Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.
- Procedures for monitoring subject compliance.

Assessment of Efficacy

- Specification of the efficacy parameters.
- Methods and timing for assessing, recording, and analyzing efficacy parameters.

Assessment of Safety

- Specification of safety parameters.
- The methods and timing for assessing, recording, and analyzing safety parameters.
- Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.
- The type and duration of the follow-up of subjects after adverse events.

Statistics

- A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).
- The number of subjects planned to be enrolled. In multicenter trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.
- The level of significance to be used.
- Criteria for the termination of the trial.
- Procedure for accounting for missing, unused, and spurious data.
- Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).
- The selection of subjects to be included in the analyses (e.g., all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

Direct Access to Source Data/Documents The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

Quality Control and Quality Assurance

Ethics: Description of ethical considerations relating to the trial.

Data Handling and Recordkeeping

Financing and Insurance: Financing and insurance if not addressed in a separate agreement.

Publication Policy Publication policy, if not addressed in a separate agreement.

72. Explain the three key aspects in set up of ad-hoc studies?

73. What are the operational principles in conducting PE trend studies