INDEX

NAME:_____ STD.:_____ SEC.:_____ ROLL NO.:_____ SUB.:_____

S. No.	Date	Title	Page No.	Teacher's Sign / Remarks
		Dr. Dhulipalla Nagalatha		
		Dr. Dhulipalla Nagalatha Asst. Professor Department of Pharmacy Practice SIP.		
		Pharmacoepidemiology.		
		1) Introduction of PE		
		2) origin & Evaluation of PE		
		3) Aim & Applications.		
		4) Outcome measure & drug use measure		
		5) Prevalence, Incidence & R.R.		
		6) Monetary units, No. of Prescriptions, units of drug's dispensed, DDD, PDD.		
		7) medication adherence measurement		
		8) Measurement of risk.		
		9) attributable risk, R.R, T.Risk relationship, Odds ratio.		
		10) DUR, case reports, case series. Surveys of drug use, cross sectional studies. Cohort Studies, case control studies, case-cohort studies, meta-analysis studies. Spontaneous reporting, PEM, Record Linkage system.		
		11) Ad Hoc data sources & Automated data systems.		

S. No.	Date	Title	Page No.	Teacher's Sign / Remarks
		12) Studies of vaccine safety		
		13) Hospital Pharmacoepidemiology		
		14) PE & risk management		
		15) Drug induced birth defects.		
		16) Pharmacoeconomics		
		17) Definition, history, need of PE Evaluations.		
		18) Role in formulary management decisions		
		19) outcome assesment & Types of Evaluation		
		20) Cost minimization		
		21) Cost benefit		
		22) cost effectiveness.		
		23) Cost utility.		

Pharmacoepidemiology: PE

Definition:

It is the study of the use of and Effect of medicines in large number of people.

→ It bridges blw clinical Pharmacology & clinical Epidemiology.

→ PE studies may examine a single individual to huge groups of people followed for many years.

Potential contributions of Pharmacoepidemiology:

→ Information which supplements the information available from Premarketing studies.

→ new types of information not available from Premarketing studies.

Study designs available for PE studies.

Randomized clinical trials
↕
Prospective cohort studies
↕
Retrospective cohort studies.
↕
Case-control studies.
↕
Analysis of secular trends.
↑
Case series.
↕
Case reports.

Down to up

→ The scope of pharmacoEpidemiology will first be compared to that of clinical Pharmacology and then go to Epidemiology.

(2)

→ It involves in gathering & analysis of information in order to identify possible causation & related factors

→ In genelal pharmacoEpidemiology Examines the
* Relationship blw the drug exposure & health outcomes in a defined population.

Origin & Evaluation:

→ ADR's to drugs were as old as modern pharmacotherapy which was developed in 20th century.

→ Drug Resistance, drug abuse & variations in rates of clinical effectiveness were the other therapeutic problems which Emelged.

→ In 1961 the case reports of maternal use of thalidomide with malformations in offspring results in awarness of the potential for drugs to cause ADRs.

→ Since then a greater attention was focused on the detection, prevention & management of ADRs & the Era of PharmacoEpidemiology has begun.

→ Important ADRs detected

Eg: Grey baby syndrome
Isotretinoin induced birth defects
Suicidal ideation with Fluoxetine
Venous thromboembolism with oral contraceptives
Deaths with terbutaline.

→ In Early 1960, the related field of drug utilisation way developed along with the study of ADRs. (3)

→ Previously DU studies were conducted mostly for marketing purposes and data were not available for use by health authorities.

→ According to WHO, DU is the marketing, distribution, Prescription & use of drugs in a society with special Emphasis on the resulting medical, social & Economic Consequences.

→ Europe, DU Research developed → National
International level

→ In NA, DU - Research developed smaller scale.
& on Prescribing antibiotics.

→ DUR is an authorized, structured, & continuing program that reviews analyses & interprets Pattern of drug use against Predetermined Standards.

Why Pharmacoepidemiology: ?

→ lack of alternative models to investigate some drug events. Eg: Teratogenic effects of a new medicine - Evaluation.

→ adequate for Establishing Effectiveness, the sample size are inadequate to detect less common ADRs.

→ PE models provide alternative approaches to evaluate drug effects.

→ Investigate the single Indication.

Aims of Pharmacoepidemiology:

→ ① **Signal generation:** most commonly associated with ADR but also use to detect new applications.

Eg: minoxidil 1st indicated for HTN but case report soon identified it causes hirsutism in a no. of patients, side effect was investigated.

→ ② **Risk Quantification:** of ADR often require large sample size

→ The Rule of three.

Indicates if an event occurs 1 of every 50,00. Exposed persons.

3 x 5000 people would be needed in sample to be 95.

→ ③ **Hypothesis testing:**

→ It requires use of comparison groups to determine whether there are differences in variables of interest.

Applications of PE:

→ ① Estimation of the risk of drug use.

Eg: Risk involved in drug use can be quantified.

The benefits & Risks of use of a drug may be weighed

Risk estimation also helps to identify risk situation.

Eg: Case report of Alprazolam induced psychiatric disturbances appeared soon after its introduction to market.

→ ② **use in Patient counselling:** Other

→ Collection & analysis of observational data from studies may help to address certain issues through counselling the patients.

→ ③ Formulation of Public health policy decisions.

→ Qualitative as well as Quantitative information.

→④ Formulation of therapeutic guidelines and discovery of new indications.

→⑤ Facilitation of Pharmacoeconomic Evaluation.

Measurement of outcomes in Pharmacoepidemiology

(5)

Out come measures include the studies on.

1) Functional Status
2) Symptom Status.
3) Patient satisfaction with various aspects of care
4) QoL (Quality of life studies)

→ Therapeutic out comes may be classified as.

1) Cure
2) improvement
3) No change (or) deterioration.

→ On the other hand they can be classified as "success (or) fail

→ In any event clinical judgement is required in Establishing outcomes.

" morbidity & mortality are the most commonly used measures of outcome."

Morbidity: It is measured as the no. of cases of disease or Events that occur per unit of population (per 100) unit of time (per year) or both (events/100/year).

→ The measurement of outcomes in PEY can be done by two approaches.

1) Out come measures
2) Drug use measures.

1) Out come measures:	2) Drug use measure
1) Prevalence 2) Incidence. 3) Incidence Rate	1) Monetary units (6) 2) No. of Prescription 3) Units of drug dispensed 4) Defined daily doses 5) Prescribed daily doses. 6) Medication adherence measurement.

1) Prevalence:

→ It is concerned with disease status.

→ It is the proportion of people affected with a disease (&) Exposed to a particular drugs in a population at a given time.

→ Prevalence varies b/w 0-1. it can also be Expressed as %.

eg: Prevalence of Schizophrenia is 1% in Europe.

Prevalence = a/b.

a - no. of population with disease at a given time.

b - total no. of population at a given time.

2) Incidence: (Cumulative incidence)

It is the number of new cases with a specified time period divided by the size of the population initially at risk.

C.I = no. of new cases in a specified time period / size of the population initially at risk.

Incidence Rate:

→ It is the number of new cases per unit of person time at risk.

→ It describes the probability of a new case occuring during a given time interval.

$$IR = \frac{\text{No. of new cases of disease during a period of time}}{\text{Person time at risk}}$$

Person time: Estimate of the actual time at risk in years, months, or days that all persons contributed to study.

2) Drug use measures:

1) Monetary units:

→ Drug use has been measured in monetary units to quantify the amounts being consumed by population.

→ Monetary units are convenient & can be converted to a common unit, which then allows for comparison.

Disadvantage: ~~It quantifies~~.

→ Quantities of drugs actually consumed are not known & prices may vary widely.

2) Number of Prescriptions:

→ It has been used in research due to the availability & ease.

disadvantage: Quantities dispensed vary greatly as duration of treatment.

3) Units of drug dispensed:

→ Units of drug dispensed like tablets, vials is easy to obtain & can be used to compare usage trends within population.

Disadvantage: No information is available on the quantities actually taken by the patient.

→ Hence difficult to determine the actual no. of patients exposed to the drug.

4) Defined daily doses: (DDD)

→ It is the estimated average maintenance dose per day of a drug when used in its major indication.

→ It is normally expressed as DDD/1000 patients/day (or) DDD/100 bed/day.

→ It is helpful in describing & comparing patterns of DU & provides denominator data for estimation of ADR rates.

Advantages:

→ Its usefulness for working with readily available drug statistics.

→ It allows comparison b/n drugs in the same therapeutic class.

Disadvantages:

→ Problem arises when doses vary widely like with antibiotics. or if the drug has more than 1 major indication

Eg: Acetyl salicylic acid.

Low dose - avoid cardiac effects.
Modelate dose - Pain management.
High dose - Inflammatory condition.

5) Prescribed daily doses:

→ It is the average daily dose of a drug that has actually been prescribed.

Disadv:

→ Not useful to estimate incidence & prevalence of drug use

→ (a) To quantify (&) Identify Patients who receive doses lower (&) higher than those considered effective & safe.

→ It does not indicate no. of population Exposed to drug. However it provides estimate of no. of Person-days of Exposure.

6) Measurement of medication adherence:

Definition:

The Extent to which a Patients behaviour coincides with the intention of health advice given.

① Biological Assays:

→ Biological assays measure the Conc^n of a drug, its metabolites, (&) tracer compounds in the blood (&) urine of a patient.

→ These measures are intrusive & often costly to administer.

→ Patients who know that they will be tested may consciously take medication that they had been skipping So, the tests will not detect individuals who have been non adherent.

→ Drug (&) food interactions, physiological differences, dosing schedules and the half life of the drugs may influence the results.

→ Biological tracers that have known half lives and don't interfere with the medication may be used but there are ethical concerns.

→ All of these methods have high costs for the assays that limit the feasibility of these techniques.

2) Pill counts:

→ Counting the no. of pills remaining in a patients supply & calculating the number of pills that the patients has taken since filling the prescription is the easiest method for calculating patient medication adherence.

→ Some data indicate that this technique may underestimate adherence in older populations.

→ Patients of non adherence are often difficult to discern with a simple count of pills on a certain date weeks to months after the prescription was filled.

3) Weight of topical medications:

→ The weight of a topical medication remaining in a tube is used as a measure of adherence.

→ When compared with patient log books of daily medication use, weight estimates of adherence were considerably lower than patient log estimates.

→ In the clinical trials involving topical applications incorporate medication weights as the primary measure of adherence.

→ In a comparison of methods to measure adherence found that estimates calculated from medication logs & medication weights were consistently higher than those of electronic monitors

4) Electronic monitoring:

→ The medication Event monitoring system (MEMS) manufactured by Aardex corporation allows the assessment of the no. of pills missed during a period as well as adherence to a dosing schedule.

→ The system electronically monitors when the pill bottle is opened, and the researcher can periodically download the information to a computer.

disadv: The availability & cost of this system could limit the feasibility of its use.

5) Pharmacy Records & prescription claims

→ This method can be used primarily for medications that are taken for chronic illnesses. (such as HTN)

→ These records provide only an indirect measure of drugs consumed.

disadv: Patterns of over & under consumption for periods less than that between refills cannot be assessed.

6) Patient interviews:

→ Studies have consistently shown that third party assessments of medication adherence by healthcare providers tend to over estimate patients adherence.

→ Interviewing patients to assess their knowledge of the medications they have been prescribed and the dosing schedule provide little information as to whether the patient is adherent with the actual dosing schedule.

→ Subjective assessments by interviewers can bias adherence estimates.

→ This method is rarely used in medical research to assess adherence.

① Patient Estimates of adherence:

- Direct questioning of patients to assess adherence can be effective method.
- However the patients who claim adherence may be underreporting their non adherence to avoid caregiver disapproval.
- Other methods may need to be employed to detect these patients.

(12)

Concept of risk in Pharmacoepidemiology.

Measurement of risk:

→ The risk of an ADR is expressed in many ways.

1) Attributable risk
2) Relative risk
3) Time-risk relationship
4) Odds ratio.

(13)

1) Attributable risk:

→ useful approach to express the magnitude of problems. also called as the risk difference or excess risk.

→ It is the difference blw the risk in the exposed group & the base line risk in unexposed population.

$$\text{Attributable Risk} = \left(\frac{a}{b}\right) - \left(\frac{c}{d}\right)$$

$$AR = \frac{\text{Incidence of disease rate among Exposed} - \text{Incidence of disease rate among nonExposed}}{\text{Incidence disease rate among Exposed.}} \times 100$$

Uses:

→ allows the investigator to determine how morbidity & mortality are effected by removing the Exposure.

→ Provides information on the type of effect that can be acheived by useing & Eliminating the exposure.

2) Relative Risk: (RR)

It measures how likely the exposed group will develope a disease compared to the unexposed group.

$$RR = \frac{\text{Incidence in the exposed}}{\text{Incidence in the unexposed}} = \frac{a/a+b}{c/c+d}$$

Example.

		Lung cancer.		
		Yes	No	Total
Smoking	Yes	70	300	370
	No	15	700	715
	Total	85	1000	1085

(14)

$$RR = \frac{70/370}{15/715}$$

3) Time-Risk relationship:

-) The risk should ideally be expressed as function of time.
-) The risk must be atleast be Estimated for different time segments.
-) In practice this may be difficult since the type of function may not be used the exposure duration in a large number of cases can be investigated.

Example.

Risk	Yes	No	Total
Exposed	A	B	A+B
No Exposed	C	D	C+D

(15)

Odds Ratio:

→ Odds Ratio is a measure of strength of association blw the risk factor & outcome.

→ The derivation of the odds ratio is based on three assumptions.

a) the disease being investigated is relatively rare.

b) The cases must be representative of those with the disease.

c) The controls must be representative of those without the disease.

$$\text{Odds Ratio} = \frac{ad}{bc}$$

Risk	Yes	NO
Exposed	A	B
Not Exposed	C	D

Role of PE in Risk management:

→ to identify & to measure ADR
→ To improve drug safety monitoring
→ To inform Prescribing Physicians.
→ To Ensure better Patient care.
→ To identify Early detection & Early prevention of occulence of ADR.

Pharmacoepidemiological methods.

→ Various Pharmacoepidemiological methods include.

1) Qualitative models : analyze safety & effectiveness in economic way
   1) case reports
   2) case series
   3) survey of drug use
   4) cross sectional studies
   5) cohort studies & case control studies
   6) meta analysis
   7) Spontaneous Reporting.
   8) Prescription Event monitoring.
   9) Drug utilization review.
   10) Record linkage system.

Advantages :

→ These studies study people over a period of time & study effect of drugs over people.

→ Can generate effective data.

→ These studies alert clinicians manfacturers & regulators of potential problems.

→ Helpful for monitoring drug are by clinicians & other health care authorities.

→ Have great flexibility of sources of data.
   ↳ i.e Patient records, patient charts, Computerized data base

① Case reports:

→ Case reports are simply reports of events observed in single patients.

→ Case report describes a single patient who was exposed to a drug & experiences a particular, usually adverse outcome.

Eg: Case report published about a young woman who was taking oral contraceptives & who suffered a pulmonary Embolism.

→ Case reports are useful for raising hypotheses about drug Effects, to be tested with more rigorous study designs.

Disadv: However in a case report one cannot know if the Patient reported is either typical of those with the Exposure (&) typical of those with the disease.

→ Certainly one cannot usually determine whether the adverse outcome was due to the drug Exposure (&) would have happened anyway. As such it is very rare that a case report can be used to make a statement about causation.

→ One Exception to this would be when the outcome is so rare and so charcteristic of the Exposure that one knows that it was likely to be due to the Exposure even if the history of Exposure were unclear.

2) Case series:

→ It is collection of patients, all of whom have a single exposure, whose clinical outcomes are then evaluated & described.

→ Often they are from a single hospital (&) medical practice.

→ Alternatively case series can be collection of patients with a single outcome.

Eg: 100 consecutive women under the age of 50 who suffer from a pulmonary embolism and note that 30 of them had been taking oral contraceptives.

After drug marketing case series are most useful for two related purposes.

1) They can be useful for quantifying the incidence of an adverse reaction.

2) They can be useful for being certain that any particular adverse effects of concern does not occur when observed in a population which is larger than studied prior to drug marketing.

3) Cross sectional studies:

→ A cross sectional study measures the prevalence of health outcomes or determinants of health & both in a population at a point in time (&) over a short period.

→ They are usually done through surveys, chart reviews, (&) data base analyses.

→ They provide a view of the state of affairs at that time, & provide an estimate of the prevalence of utilization & of outcomes.

→ Such information can be used to explore aetiology.
Ex: The relation b/w cataract and vitamin status has been examined in cross sectional surveys.

→ These types of studies have been used to compare drug use between countries or regions with in a country.

→ very large differences suggest that reasons for those differences should be investigated & policies examined to determine whether outcomes & costs also differ & whether changes should be made.

→ However associations must be interpreted with caution. Bias may arise because of selection into (&) out of the study population.

Eg: A cross sectional survey of asthma in an occupational group of animal handlers would under estimate risk if the development of respiratory symptoms led people to seek alternative employement & therefore to be excluded from the study.

→ A cross sectional design may also make it difficult to establish what is cause & what is effect.

4) Cohort Studies:

→ The term cohort refers to a group of individuals that share common characteristics (Eg: age, birth)

→ The main objective of cohort study is to compare & measure the outcomes of an exposure in blw two groups & applying it in present practice.

→ Measures the frequency (Descriptive)

→ To describe the incidence rates of an outcome over time, & simply describe the natural history of disease

→ measures of association, (Analytical)

→ To ~~does~~ analyze the associations blw the rates of the outcomes & risk factors.

→ Identify subsets of a defined population & followed them over time, looking for differences in their outcome

→ used to compare Exposed Patients to unExposed Patients

→ Done either prospectively (&) retrospectively.

→ Requires large sample size & can require prolonged time period to study delayed outcomes.

Difference blw Cohort study & case control study

Case control studies
↓
Disease
Present (cases) | Absent (controls)

Cohort Studies
↓
Factor · Present (Exposed)
Absent (unexposed)

5) Case control Studies:

→ compare cases with the disease to controls without the disease looking for differences in Exposure.

→ Multiple possible causes of a single disease can be Studied.

→ Helps in studying relatively rare disease requires smaller sample size.

→ Informations are generally obtained retrospectively from the medical records by interviews or questionnaires.

→ Limitations are validity of retrospective information & selection of control is challenging task. Inappropriate control section can lead to incorrect conclusion.

6) Case - cohort Studies:

→ In a case - cohort study, cases are defined as those participants of the cohort who developed the disease of interest, but controls are identified before the cases develop.

→ Case cohort studies are very similar to Case control studies.

7) Surveys of drug use:

→ Simplistic approach

→ Provide crude utilisation data for large areas.

→ Sales data such as no. of prescriptions dispensed (&) total no. of pills.

→ Hence also called as drug use surveys. (&) Single group Cohort studies.

→ make use of DDD & PDD.

8) meta-analysis studies:

→ meta analysis is a method which can be used to combine the results of two (&) more studies.

→ It is defined as a quantitative method of pooling information.

→ It is a quantitative study where in a set of statical procedure is used to summarize the results of a number of independently conducted research studies.

→ Its a time consuming & usually conducted by team of researchers.

→ meta analysis is the statistical analysis of a large collection of analysis results for the purpose of integrating the findings.

metaanalysis.

Retrospective	Prospective
→ Selection of the target Population → The nature of the intervention. → The choice of comparator → The outcomes to be assessed & their measures.	advantages. → Enabling prospective application of study criteria. → Enabling a priori statements of intended analyses. including subgroup analyses to be made before the results of individual trials are known.

9) Spontaneous Reporting:

→ It involves identification of and informing the Pharmacovigilance bodies of an ADR (&) an ADE by medical professionals (physicians, dentists, nurses, Pharmacists)

→ Spontaneous reports are termed spontaneous as they take place during the clinicians normal diagnostic appraisal of a patient. when the clinician is drawing the conclusion that the drug may be implicated in the causality of the event.

→ To identify and report any adverse events to their national Pharmacovigilance centre. health authority & to the drug manufacturer itself.

Disadv: → under reporting where unlike in clinical trials, less than 100% of those adverse events occurred are reported (type A & type adrs)

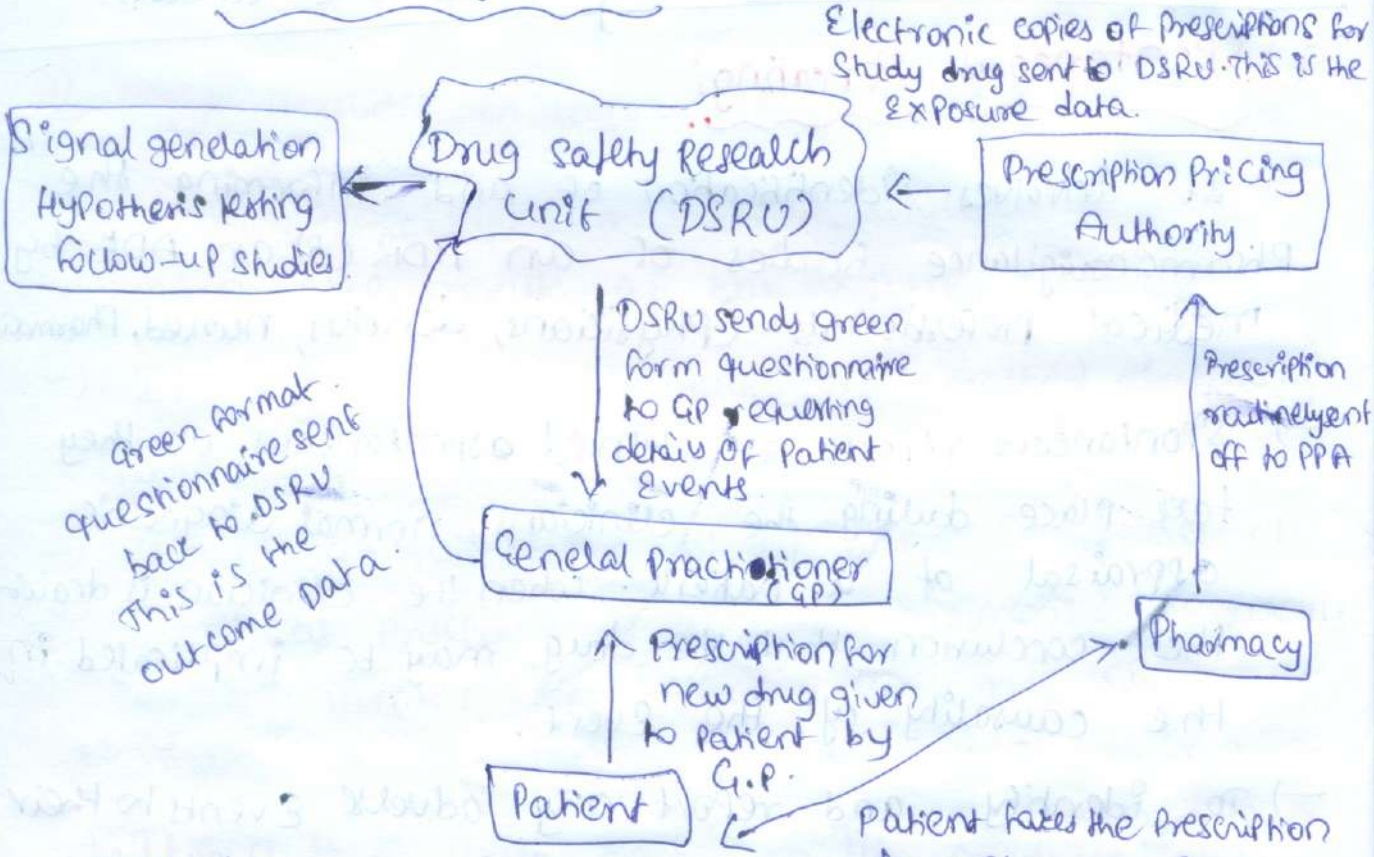
Advantages: → very wide spectrum → continuous
→ Effective → comparatively cheap
→ Rapid.

10) Prescription Event monitoring: [PEM]

→ PEM is a non-interventional, observational cohort form of Pharmacovigilance.

→ In PEM, the exposure data are national in scope throughout the collection period & unaffected by the kind of selection & exclusion criteria & characterise Clinical trials data.

Process of PEM



methods:

→ New drug licence, DSRU decides whether to monitor drug

→ Green forms sent to GPs

→ Green forms returned to DSRU.

→ Data entered onto computer.

→ Pregnancies, causes of death, Serious possible ADRs and events of interest followed-up.

→ Confidentiality & security carefully maintained.

advantages:

- → calculation of incidence density
- → carried out on a national scale
- → comparison of reasons for withdrawl and incidence density.
- → outcome of exposed pregnancies
- → signal genelation & exploration.
- → delayed reactions can be detected
- → disease investigation.

disadvantages:

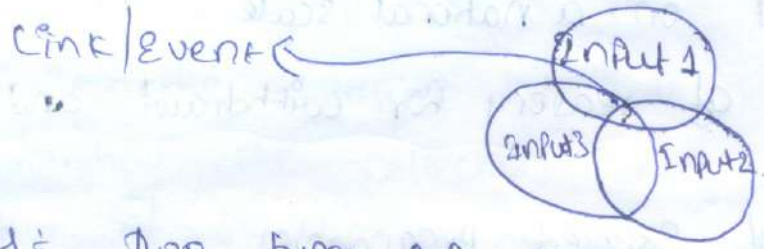
- → No method of measuring compliance
- → No method to determine the non prescription medication.
- → Non return of green forms.
- → does not extend to hospital monitoring
- → Data collection is an operational difficulty.

ii) Record Linkage system:

→ Record Linkage is the process of bringing together two or more records relating to the same individual (person) family or Entity (eg: Event, object, geography, business etc).

⇒ To find syntactically distinct data Enters that refer to the same Entity in two & more input files.

→ Part of the data cleaning process, which is a crucial first step in the knowledge discovery process.



Types: Two types of strategies.

→ Deterministic

→ Probabilistic.

① Deterministic:

→ A pair of records is said to be a link if the two records agree exactly on each element within a collection of identifiers called the match key.

→ All (&) none.

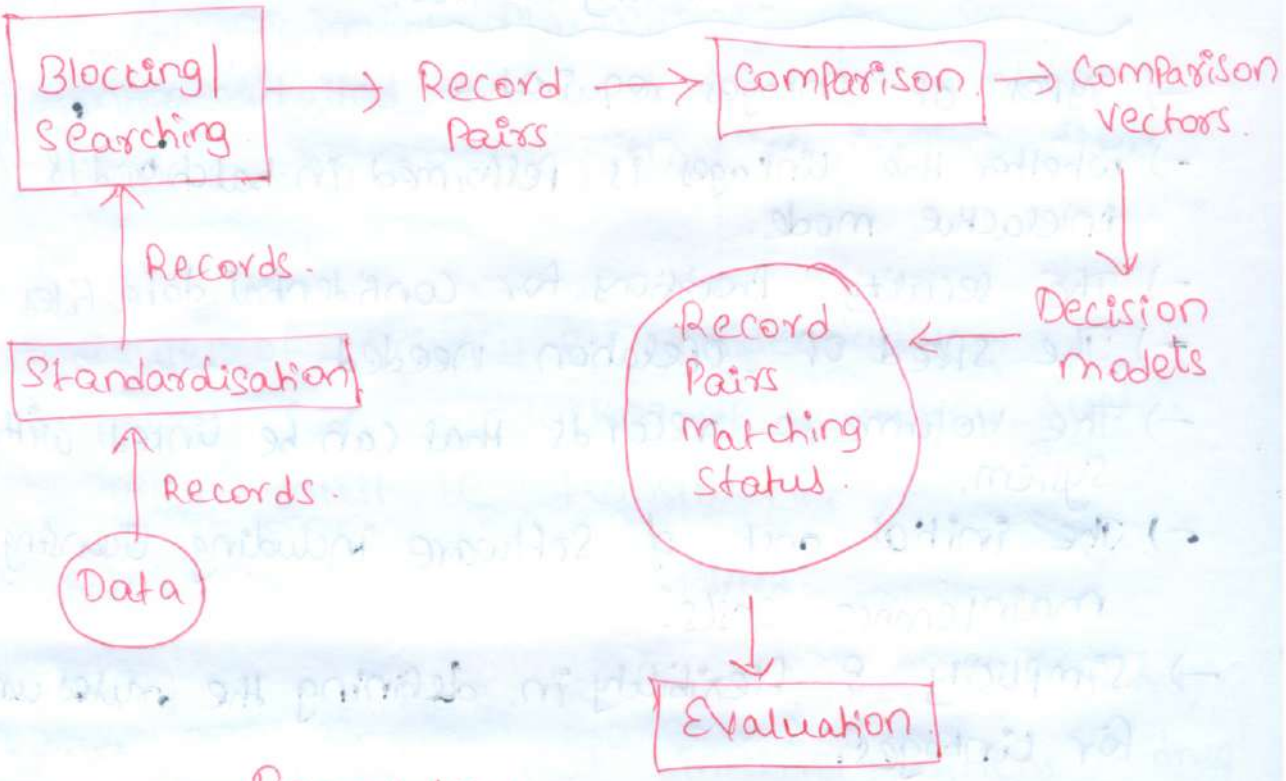
Ex: when comparing two records on last name, street name, year of birth & street number the pair of records is deemed to be a link only if the names agree on all characters, the years of birth are the same and the street numbers are identical.

② Probabilistic:

→ Pairs of records all classified as links, possible links, or non links.

→ Here we consider the probability of a match in the given observed data.

→ In Probability matching, a threshold of likelihood is set (which can be varied in different circumstances) above which a pair of records is accepted as a match, relating to the same person & below which the match is rejected.



Record Linkage System.

Standaldization:

→ In every data there exist many manual errors & non matching abbreviations etc. which may present themselves as seperate data without actually being so

→ First step

→ To clean & standaldise the data.

Blocking: → In order to reduce the search space (i.e the number of record pairs to be compared)

→ To group similar records together, called blocks (or) clusters.

→ The data sets are split into smaller blocks & only records with in the same blocks are compared.

Matching:

→ Exact matching: Linkage of data for the same unit.

→ Statistical matching: attempts to link files that may have few units in common.

Requirements for defining a RLS:

→ Types of linkages required

→ whether the linkages is performed in batch and/& interactive mode.

→ The security provisions for confidential data files.

→ The speed of operation needed

→ The volume of records that can be linked with the system.

→ The initial cost of software including licensing & maintenance costs.

→ Simplicity & flexibility in defining the rules used for linkages.

Uses:

→ used to improve data quality & coverage. for long term medical follow-up of cohorts.

→ for Building new data soulces & for a large of other statistical purposes.

→ It helps create statically relevant soulce of new information.

→ Answers research questions relating to genetics occupational & Environmental health & medical research.

Applications:

→ Duplication in data in minimized.
→ Powerful tool for generating more value out of existing databases
→ large projects regarding the census of an entire country can be planned.
→ more detailed information can be obtained.
→ Becomes easier to follow cohorts.

Drawback:

→ Issues of privacy & confidentiality.
→ policies for conducting studies using such system must be transpalent.

12) Drug utilization Review: (DUR)

→ DUR programs have been defined as "structured, ongoing initiatives that interpret patterns of drug use in relation to predetermined criteria & attempt to prevent or minimize inappropriate prescribing.
→ DUR programs differ from drug utilization studies which are time limited investigations that measure drug use, but do not necessarily assess appropriateness & attempt to change practice.
→ Recently the use of clinical decision support with in computerized prescriber order entry (CPOE) programs has risen dramatically.
→ The use of such programs to improve prescribing can be considered a form of prospective DUR in which prescribers are the targets of interventions

→ Generally the DUR Process involves comparing actual behaviour to Explicit, Prospectively Established Standards refelled to as criteria.

→ After developing criteria the next step in the DUR Process is to measure adherence to explicit criteria by examing individual level.

→ Instances in which medication use does not agree with criteria are called Exceptions.

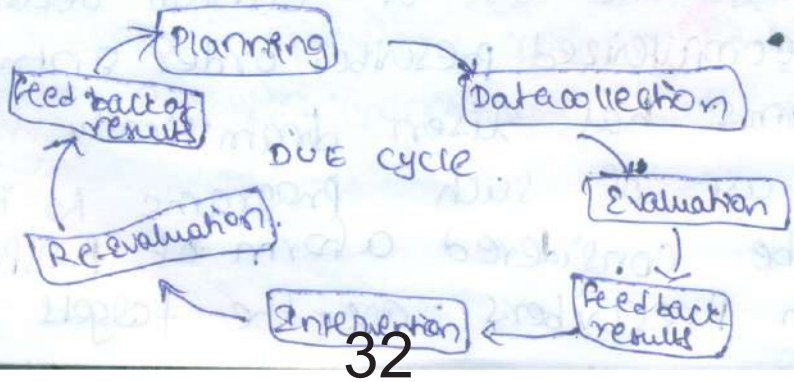
→ Next interventions are implented where appropriate often following an implicit review.

→ There are different settings, in which the DUR model is applied.

→ Out Patient retrospective DUR Programs use computerized administrative data. (i.e Pharmacy & medical claims data maintained for billing)

→ To identify exceptions that all then reviewed by a physician (&) Pharmacist & by a committee of health professionals & result in an intervention. (Eg: a mailed alert letter to the physician)

→ The alert letter typically describes the DUR Program and the criterion & provides literature references supporting the criterion & a patient profile demonstrating that the criterion was violated.



5) Ad Hoc data sources:

→ The data sources available for pharmacoepidemiological studies as Ad hoc sources.

→ Ad hoc sources are those that are collected during post marketing surveillance studies.

→ Adhoc is something which is for (&) concerned with one specific purpose. i.e providing data regarding drug safety in long term use or which concerns about the drug aspects in a large population which is seen in post marketing studies compared to pre marketing studies.

Limitations of premarketing clinical trials:

→ Size of the patient population studied

→ Narrow population - often not providing for special groups

Elderly, children, women, Ethinicity

→ Short dulation.

Objectives of post marketing surveillance:

→ Rare adverse Effects

→ Adverse event in pts different from the study subjects

→ long term Effects

→ Effectiveness of the drug for the original indications.

→ other beneficial Effects of the drugs

Different Ad hoc Data Sources:

→ Spontaneous reporting
→ Global drug surveillance: The WHO Programme for international drug monitoring
→ Case control surveillance
→ Prescription Event monitoring.

a) Spontaneous Reporting:

Determinants of the level of performance of a spontaneous reporting system is based on

→ Reporting rate. (Eg: no. of case reports/million/yr)
→ Reporting distribution. (Eg: specialists, GP, Pharmacists)
→ Reporting quality (Documentation & follow-up)
→ Reporting Efficiency. (Proportion of relevant case reports. Eg: concerning unknown & serious adverse Effects)

→ The data collection of spontaneous reporting through voluntary & mandatory services is done by MEDWATCH Programme.

↳ is for health professionals & the public to voluntarily report serious reactions & problems with medical products, such as drugs & medical devices.

Limitations: → causal relationship in case reports usually uncertain
→ underreporting & reporting bias.
→ No quantitative measurement
→ Insensitive to type 'C' adverse Effects.

b) Global drug Surveillance:

→ WHO Quarters in Geneva is responsible for the WHO drug monitoring programme.

Functions:

→ Identification & analysis of new ~~drug~~ adverse reaction signals from the case report information submitted to the national centres, & sent from them to the WHO ICSR database.

→ Provision of the WHO database as a reference source for signal strengthening & ad hoc investigations.

→ ~~Investigation~~ Information Exchange b/w WHO & national centres, mainly through Vigimed, an e-mail information Exchange system.

→ Publication of periodical newsletter, guidelines & books in the pharmacovigilance & risk management area.

→ Supply of tools for management of clinical information including adverse drug reaction case reports.

→ Computer software for case report management designed to suit the needs of national centres. (Vigiflow)

→ methodological research for the development of Pharmacovigilance as a science.

→ Annual meetings for representatives of national centres at which scientific & organizational matters are discussed.

Automated data bases:

→ The ideal data base would include records from.
  → Inpatient & out patient care
  → Emergency care
  → mental health care
  → All laboratory & radiological tests.
  → All prescribed & over the counter medications
  → alternative therapies.

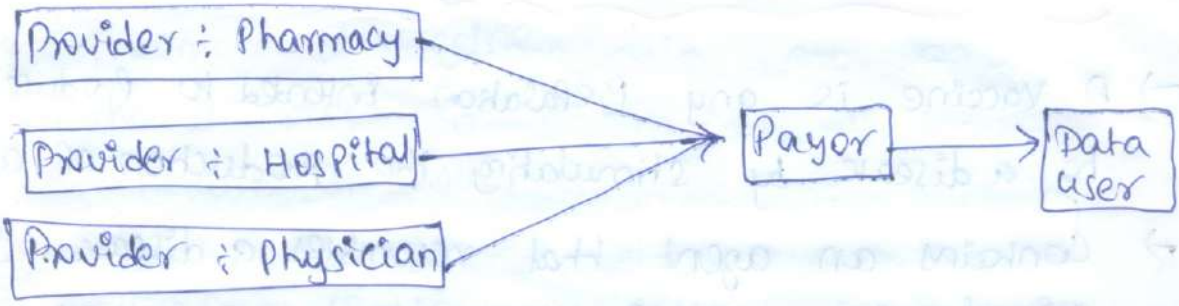
Eg:- of automated data bases.

1) Group Health cooperative
2) kaiser permanente medical care program.
3) HMO Research network
4) United health group
5) medicaid databases.
6) Health services databases in Saskatchewan
7) automated Pharmacy Record linkage in the Netherlands
8) Tayside medicines monitoring unit (MEMO)
9) UK General Practice Research Database (GPRD)

→ large Electronic databases can often meet the need for a cost effective & efficient means of conducting post marketing surveillance studies.

→ for claims, for clinical services & therapies. automated data bases are used.

→ Claims data arise from a persons use of the health care system.



Applications of database:

→ When looking for uncommon outcomes because of the need for a large sample size.
→ When a denominator is needed to calculate incidence rates.
→ When one is studying short term drug effects.
→ When time is limited.
→ When budget is limited.

Uniquely problematic situations include:

→ illness that do not reliably come to medical attention
→ Inpatient drug exposures that are not included in some of these data bases.
→ Outcomes that are poorly defined by the ICD-9cm coding system such as Stevens-Johnson syndrome
→ Descriptive studies, since the population might be skewed.
→ Important medication exposure information that is not available - Particularly over the counter medications.

Studies of vaccine safety:

→ A vaccine is any preparation intended to produce immunity to a disease by stimulating the production of antibodies.

→ Contains an agent that resembles a disease - causing microorganism, & is often made from weakened & killed forms of the microbe or its toxins.

→ The most common method of administering vaccines is by injection but some are given by mouth &, nasal spray.

→ Among the most cost effective & prevalent public health interventions.

→ No vaccination is 100% safe.

aims of immunisation:

→ To protect those at highest risk.

→ To Eradicate, Eliminate (&) control disease.

Cullently it is Estimated that vaccination saves the lives of 3 million children in a year.

Eradication: Infection has been removed worldwide: Eg: smallpox

Elimination: Disease has disappeared from one area but remains Elsewhere Eg: Polio, measles.

Control: Disease no longer constitutes a significant Public health Problem Eg: neo-natal tetanus.

→ vaccine give specifically to those at increase risk of disease.

- High risk groups
  Eg: Pneumococcal vaccine
- Occupational risk
  Eg: Hepatitis B, Influenza
- Traveller's
  Eg: Yellow fever, Rabies, meningitis
- Outbreak control
  Eg: Hepatitis A, vaccine, measles.

Ideal Vaccine:

- Immunogenic.
- Long lasting immunity
- Safe
- Stable in field conditions
- Combined.
- Single dose.
- Affordable to all.

Much needed vaccines for the developing world.

- Malaria
- Tuberculosis
- HIV
- Hookworm
- Dengue
- Enterotoxigenic E.coli
- Shigella.

Therapeutic vaccine: Identification of specific tumour antigens provide immune targets. For which immunogenic vaccines may conceivably be designed.
Eg: Leukemia, Breast cancer, melanoma, prostate cancer colon cancer.

→ Similarities blw vaccines & other drug

→ vaccines are also medicines.
→ Potential for adverse effects.
→ multiple ingredients
→ Potential for interaction ε disease & other medicines
→ also need to comply with standards of Safety, Efficacy, & quality.

Surveillance of Vaccine Preventable disease:

→ vaccine uptake
→ Vaccine Effectiveness.
→ Serological Surveillance
→ Adverse events
→ knowledge & attitudes
→ vaccine uptake
→ Disease incidence.

Vaccine Evaluation:

→ Pre-licensing : Randomised, Blinded, controlled clinical trials.
→ Post-licensing : Observational studies
→ vaccine Efficacy : Protective Effect under, Idealised conditions
→ vaccine Effectiveness : Protective Effect under, ordinary conditions of a Public health Programme.

RCT : Controlled Experiments, simple interpretation.
Prone to bias, more complex interpretation.

Hospital Pharmacoepidemiology

need of Hospital PE:

- Tracking the drug administered to the patient during the Entire stay in the hospital.
- Systematical recording of ADR.
- Creation of databases has helpful the storage of large number of patient data over longer period of time.

Clinical Problems in PE-Research

- Volume & charcteristics of hospital admission → major diseases.
- Charcteristics of hospitalized patients & hospitalized drug use.
  - Older age
  - Sickness.
  - Multiple concullent diseases.
- PTs with Polypharmacy during hospital stay has greated risk of drug interaction.
- Prescribing suboptimal drug regimens.
- Inadequate Laboratory monitoring.
- PE says that most drug reactions occurs on the first 5 days on a drug. Hefefore surveillance during this. Period helps to detect ADR.
- Methodological Problems in PE Research
  1) Logistic issues
  2) Methodlogic issues.

Logistic issues: - major challenge for PE developing complete Information on total drug Exposure during hospital stay.

- Computerized Prescriber order Entry (CPOE).

Methodologic Issues:

- Issue of uncertain validity of the drug information in the hospital medical record.
- Issue of uncertain validity of diagnosis information in hospital medical record.
- Issue of absence of inpatient information on the absence of outpatient information.
- Tendency to record only the most extreme & dramatic events.
- Referral bias will be present.
- Problems from hospital staff participation.
- Medical records are not meant for research purposes.

Inpatient database:

- Multisite database.
  - ↳ Provide support on rare drug events.

Types: commercial.
non commercial

Eg: Health Evaluation through Logical Processing (HELP)

advantages & Limitations:

- Inpatient data system are free standing instead of integrated across institution.
- Limit the ability detect events of low incidence and Produce generalizable results.
- Drug Monitoring & Drug use Evaluation Programme. finding from DUE leads to several recommendation
  1) Educating the staff
  2) Entering Patient weight into the computerized Physician Order Entry system.
  3) Aiding appropriate Prescribing through alerts & Reminders.

Pharmacoepidemiology & Risk management.

⇒ (RM)

Risk management: It represents those interventions that must be in place & must be Effective in order to shift the balance of risk to benefit from an unfavourable & unacceptable position to one that is favourable & acceptable.

→ A US FDA draft guidance described RM as an iterative process involving both assessment & minimization of risk.

→ What is the necessity of RM in prescription drug safety settings?

→ In response to challenges created by accelerated review & approval times for marketed drugs.

→ Drug product withdrawls for safety reasons

→ In prescription drug safety settings - a recent development.

Goal: To Enhance the safe use of medicines by optimizing the balance of benefit & risk.

→ Desired health Outcomes of the RM Program.

Tools to Enhance Risk benefit balance:

→ Professional labelling & Package inserts.
→ Special letters sent to health care Professionals.
→ Special educational & training Programs.
→ Patient Package inserts.
→ Medication guides.
→ use of special Packaging (Eg: blisted Packs)
→ Limitation of Prescription size.

Clinical Problems:

Risk identification & characterization:

1) Pre marketing:

→ During clinical development of a new molecular Entity a safety signal of concern arises that cannot be well answered by available studies (&) data. Large, simple, safety study (LSSS) could be considered Eg: omapatrilat, a vasopeptidase inhibitor.

2) Post marketing: most information about risk will be obtained from

→ Spontaneous (&) Published case reports of ADR's
→ National drug surveillance programs
→ Specialized Patient registries (&) ad hoc studies.

3) Product usage: Drug use data can be monitored to identify pattern of use such as.

Drug use in appropriate age groups (&) at higher doses - which require interventions to maintain an acceptable balance of risk & benefit.

4) Case reports:

→ Review of a well documented series of case reports can provide useful insight (information)
→ Spectrum
→ Severity
→ history of an adverse drug Event as well as its reversibility Predictability & Preventability.

→ main draw back: under reporting.

5) Phase IV & adhoc post marketing Epidemiologic studies relied on

→ Nature

→ absolute of safety signals arise during Preapproval Clinical Trials (&) from post marketing Spontaneous case reports.

Eg: Terodiline - torsade de Pointes

Limitations:

→ Bias - compromise the utility of safety studies.

→ methods & design of the study - leads to negative findings.

Methodologic problems:

1) Risk management goal setting:

→ Explicit - clear, unambiguous & openly stated

→ Relevant - Closely linked with the safety event of concern

→ Measurable - an attribute that permits comparison to be made and conclusions reached regarding goal achievements.

2) Risk management design & Evaluation:

→ designed - Primary goals as the focus

→ Represents intervention of uncertain & unknown Effectiveness - applied to the large number of patients.

Eg: if health outcome of interest is Prevention of fetal Exposure to a teratogen, accurate, reliable & complete ascertainment of fetal Exposure should be a design objective.

→ Implementation of an Effective RM program is necessary to Establish an acceptable balance.

Drug induced birth defects

→ A birth defect is an abnormally present at birth that affects the body structure & functions & may threaten a baby's health.

→ Birth defects can be caused by
- Environmental factors.
- Inherited factors.
- Both.

Environmental factors:
- Drugs.
- Disease / Infection
- alcohol
- caffeine, cocaine.
- Hazard Exposure during Pregnancy (Chemicals, Toxoplasmosis, X-rays)
- accidental injuries.

Factors that contribute to birth defects:
- over weight / under weight
- Ethnic / Cultural background
- Health Problems.
- Epilepsy.
- No immanizations against rubella
- STDs.

→ The potential causes of most birth defects are not known.

→ Do not take the drugs without a doctors permission.
→ Addiction is passed to a baby: baby goes through Painful withdrawl after birth.
→ Cause severe, long term behavioul & learning problems.
→ Some times infant death.
→ Stroke leading to brain damage.
→ Heart attack
→ Teratogenic effects. Eg: Phenytoin, valproic acid.
→ delayed development.
→ Sleep problems.
→ Physical & mental defects in unborn baby.

Clinical problems addressed by PE Research:

→ adverse drug effects.
→ Teratogenesis. - drug benefit / risk profile.
→ fetus is the innocent bystander with respect to its mother therapy.
→ Malformation can be avoided by the termination of Pregnancy.
→ Our understanding of a drugs teratogenic risk therefore has important consequences for how a given drug is used clinically.
→ As teratogensis cannot be predicted prior to marketing a drug.
Becoz some delayed adverse effects are not identified in Phase III clinical trials.

Currently available solutions:

1) Cohorts: Three types of cohorts

i) Studies designed to follow large populations exposed to various agents.

2) use of data sets created for other purposes.

3) Follow-up studies of selected exposures.

2) Cohorts identified from the databases

2) Case control studies.

→ Rarity of birth defects in general & of specific defects in particular, argues for the use of the case control design in PE studies of birth defects.

→ ad hoc studies.

3) Integrated approach:

1) To identify major teratogens.

2) To identify teratogens with more modest risks

→ Exposure & outcomes.

Integrated approach that combines cohort & case control studies offers an effective step towards resolving these two teratogenic concerns.

→ Studies of birth defects in the future will undoubtedly have increased attention on issues of statistical power, validity & secular changes in exposures.

→ They are to be used with relatively safety.

Pharmacoeconomics (PE)

→ challenge for health care professionals is to provide quality patient care considering economic aspects (cost) safety, & efficacy of drug therapy.

→ one among the tool that helps in decisionmaking using the combination of cost & consequences.

Definition of Pharmacoeconomics:

→ It is a collection of descriptive & analytic techniques for evaluating pharmaceutical interventions, spanning individual patients to the health care system as a whole.

→ Pharmacoeconomic techniques include

1) Cost minimization
2) Cost effectiveness
3) Cost utility
4) Cost benefit
5) Cost of illness
6) Cost-consequences

→ PE is also referred as health economics (&) health outcomes research.

History:

Roots of PE developed in 1970's following; the evolution of Pharmacy as a clinical discipline & the incorporation of the pharmaceutical sciences into pharmacy curriculum.

→ The concepts of cost-benefits & cost Effectiveness analyses were first introduced in the Pharmacy literature by in 1978 by McGhan, Rowland & Bootman et al. also published an Early research articles in 1979 in which cost benefit analysis was used.

→ Some of these major issues are, Cost Effectiveness of Pharmaceuticals for the health delivery system, Cost benefit analysis of provision of high quality of information & counselling by Pharmacists for the wellness of the American Public & Socioeconomic impact analysis of major Public Policy decision from a retrospective basis.

→ In 1983, Pathak offered a graduate level course to Provide an overview of the application of Cost benefit & Cost Effectiveness analysis in health care. at the Ohio State university college of Pharmacy.

Need for PE :

→ In industry - deciding among specific research & development alternatives
→ In government - determining Program benefits & Prices Paid.
→ In Private Sector - designing Insulance benefit coverage.
→ It can help in decision making in Evaluating the affordability of & access to the right time Comparing two drugs in same therapeutic class (3) drugs with similar mechanism of action & in Establishing accountability that the claims by a manfacturer Regarding a drug are justified.

PE identifies measures & compares the cost & consequences of pharmaceutical products & services & describe the economic relationship involving drug research, drug production, distribution, storage, pricing & used by the people.

Scenarios involved in deciding:

→ whether a drug should be included in a hospital formulary.

→ which drug would provide net positive benefit to a particular group of patients

→ which would be the best drug for a pharmaceutical manfacturer to develop & the right price to market it.

→ what is the expected quality of life improvement with a certain drug when leading off its side effects

Direct medical costs: → fixed cost.

Costs that are incurred during the provision of care.

→ used for prevention, detection & treatment of a disease.

Eg: cost of drugs, lab test, doctor fee.

Direct non medical costs: non medical services that are results of illness but do not involve purchasing medical services.

Eg: food, family care, hotel room expenses near the treatment place.

Indirect non medical costs: Include lost productivity from a disease which can manifest itself as a cost to the economy or taxation system as well as economic costs to the patient & his family.

Eg: wages & salaries lost due to morbidity & income forgone due to premature death.

Intangible costs:

These are costs included which represent other non financial outcomes of disease & medical care which are not clearly expressed in money value or rupees.

It include costs of mental agony, Pain, suffering, grief, -

Opportunity Costs:

Identify the value of opportunities which have been lost by utilizing resources in a particular service (&) health technology.

→ Costs of economic benefits forgone when one therapy is used instead of the next best alternative therapy.

-) It includes the cost of opportunity (&) revenue forgone.

-) Economic outcomes are the direct, indirect & intangible costs compared with the consequences of medical treatment alternatives.

Perspectives:

1) Patient.

2) Provider

3) Payer. (Insurance companies, Employers)

4) Society. (Pt morbidity, Pt mortality)

Applications of Pharmacoeconomics

→ aid clinical & policy decision marking.

→ quantify the value of pharmacy products & pharmaceutical care services.

→ complete pharmacotherapy decisions should contain assessments of three basic outcome areas whenever appropriate (Economic, clinical, & humanistic outcomes)

→ most drug therapy decisions were based solely on the clinical outcomes associated with a treatment alternative.

→ The current trend is also to incorporate the humanistic outcomes associated with a treatment alternative, that is to bring the patient back into this decision making equation.

→ drug therapy Evaluation.

→ clinical pharmacy service Evaluation.

→ selecting the most cost Effective drugs for an organizational formulary is important.

→ Practitioners & administrators can then use these data to make more informed resource allocation decisions.

→ Evaluating the impact a drug has on a patients HRQOL (Health related quality of life) can be useful when deciding b/w two agents for customizing a PT's pharmacotherapy.

Role in formulary management decisions:

→ PE assessment of formulary actions has become increasingly common in local, national & international formulary decision making.

→ Tactics for managing medication use include formulary management & drug policies.

Eg: PE data can support the inclusion (&) exclusion of a drug on or from the formulary & support practice guidelines that promote the most cost effective (&) appropriate utilisation of pharmaceutical products.

→ various strategies can be used to incorporate PE into formulary decision making. These include using published PE studies & economic modelling techniques & conducting local pharmacoeconomic research.

→ PE assessments of formulary decisions help to ensure that the formularies yield the highest outcome.

→ PE data well important in the management of drug benefits.

Outcome Assessments & Types of Evaluation

→ Pharmacoeconomics identifies, measures, & compares the cost consequences of drug therapy. to health care systems & society.

→ Outcome Assessments:

- Economic
- Clinical
- Humanistic

Economic: compares the costs with the consequences of the treatment.

Clinical outcomes: medical events that occur as a result of disease (&) treatment, (safety & efficacy)

Humanistic outcomes: consequence to the treatment on patient functional status (&) quality of life along several dimensions.
Eg: General health, life satisfaction etc

→ Another way categorising are Positive & negative consequences: Intermediate & final consequences.

Applications of PE:

→ formulary management
→ Individual Patient treatment.
→ medication policy determination. [drug use policy.
→ Resource allocation.
→ Disease management.

① Cost minimization Analysis:

→ It compares inputs costs of two similar interventions to ascertain which is less expensive.

→ used to compare cost per course of treatment when alternative therapies/ interventions have demonstrably equivalent clinical effectiveness.

Eg: Two drugs can be used to lower the level of blood Cholesterol. No other side effects (&) any other costs associated with the drugs.

Drug A costs NPR 2000/month. Drug B costs NPR 1500/month. Both reduces cholesterol level by the same amount.

which one should we select? why?

Fundamental assumptions:

→ two options being compared must have exactly the same effect (identical benefits)

→ The important alternatives have not been left out.

Merits:

→ Simplest of economic evaluation measures.

→ very useful method is evaluating the cost of a specific drug/ intervention.

Demerits:

→ It can only be used to compare products/ interventions with equivalent outcome or effect.

→ In many real life cases, two interventions may not always have equivalent outcomes.

→ If outcomes are measured & found to be equivalent it is a CEA.

Applications:-

→ In situations where the benefits of alternative treatments have been proven to be identical & as such this methodology is perceived as being easy to apply.

→ It is used in supporting & justifying the introduction of cheaper drugs in the same therapeutic class.

→ It is used when finding out the activity (&) output with the lowest cost.

② Cost Effectiveness Analysis:-

→ Compare cost per consequence of two (&) more interventions, where the consequences are measured by "natural" units (life years gained, saved years of life).

Outcome:

→ Compares relative costs & outcomes of different courses of action.

→ years of life saved
→ Hospital days prevented
→ No. of cases prevented
→ Reduction in cholesterol
→ Reduction in Blood pressure.

Cost Effectiveness Ratio (CER)

$$CER = \frac{\text{Cost of intervention}}{\text{Effect of intervention}} = \frac{C}{E}$$

Incremental cost-effectiveness ratio (ICER)

$$ICER = \frac{\text{Difference in cost}}{\text{Difference in effect}} = \frac{C_1 - C_0}{E_1 - E_0}$$

Applications:

→ applied to the Planning & management of many types of organized activity.

→ widely used in many aspects of life.

→ CEA has been applied to energy efficiency.

→ Thelapeutic & preventive intervention. is the ratio of the cost of the intervention to a relevant measure of its effect.

3) Cost utility analysis: CUA

→ Unlike CEA, effects in CUA are measured in terms of utility.

Quality adjusted life years. (QALYS)

Disability-adjusted life years. (DALYS)

→ It is a form of financial analysis used to guide Procurement decisions.

→ Health related quality of life is important outcome

Eg: Treatment of cancer may extend life but at the expense of side effects.

When to use CUA:

→ when intervention affects both morbidity & mortality & a common unit of outcome is desired

→ when a program being compared have a wide range of different kinds of outcomes & common unit of outcome is desired for comparison.

- Provision of ARV's Vs Polio vaccination
- Malaria Program Vs TB Program.

Steps of analysis

→ Identification of two (&) more alternatives
→ Identification of perspectives.
→ Determination of costs.
→ Determination of outcomes in utility terms.
→ Calculation of cost utility ratio.
→ Decision making.

→ outcomes may be single (&) multiple.

Determination of cost utility ratio.

Incremental cost - utility ratio

→ costs per DALY (&) cost per QALY.

$$ICUR = \frac{\Delta C}{\Delta U} = \frac{\text{Cost of Program 1} - \text{Cost of Program 2}}{\text{QALY of prg1} - \text{QALY of prg2}}.$$

Strengths:

→ Combines more than one measure of effectiveness.
→ combines both measures of mortality & 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 disease weights.
→ Problems with the quantification of patient problems

QALY:

-) The no. of years lived in Perfect health.