

■ Cost of Illness:

- Cost of illness evaluation also known as Burden of disease. It is an economic evaluation method used to identify and estimate the overall cost of a particular disease for a defined population. It involves measuring the direct and indirect costs attributable to a specific disease.
- COI is often termed as burden of illness.
- COI evaluation is not used to compare competing treatment programs or treatment alternatives.
- It is used to provide an estimation of the financial burden of a disease.
- Cost of illness studies measure the economic load of an illness or a disease.
- It estimates the maximum amount that could potentially be saved or gained if a disease or a group of diseases were to be eradicated.
- COI studies help to understand which diseases have a serious effect on their costs.
- All cost of illness studies provide important information for pharmacoeconomic studies like cost effectiveness analysis (CEA).

Applications of COI studies

- The cost of illness studies are frequently used by policy makers and other government organizations.
- In some countries the published cost of illness reports are used in law suits to recover medical insurance claims.
- They are also used to estimate the costs of fatal occupational injuries by various countries.

limitations of COI studies

- Cost of illness studies can demonstrate which diseases may require increased allocation of resources for prevention or treatment. However they are limited in determining how resources are to be allocated because they do not measure benefits.

Cost Minimization Analysis

Economic Evaluation Method:

The basic task of the economic evaluation is to identify, measure, value and compare the costs and consequences of the alternatives being considered the two distinguishing characteristics of economic evaluation are as following -

1. Is there a compare the costs of two or more alternatives.
 2. Are both costs and consequences of the alternatives examined.
- ① Full economic evaluation encompasses both characteristics, whereas a partial economic evaluation addresses only one.
 - ② Partial economic evaluations may include simple descriptive tabulations of outcomes or resources consumed and thus require a minimum of time and effort.
 - ③ Full economic evaluation includes, cost minimization, cost benefit, cost effectiveness and cost utility analyses.
 - ④ Although a full economic evaluation generally provides higher quality and more useful information, the time the resources the effort employed are also great.
 - ⑤ Application of an economic evaluation method to health care products and services especially pharmaceuticals, may increase their acceptance by health care professionals and society.

Cost Minimization Analysis:

- ① CMA involves determination of the least costly alternatives when comparing two or more treatment alternatives.
- ② With CMA the alternatives must have been assumed or demonstrated equivalency in safety and efficacy.

Once the equivalency has been confirmed the cost can be identified, measured and compared in monetary units.

- ① CMA is a relatively straight forward and simple method of comparing and competing programs or treatment alternatives as long as the therapeutics equivalence of the alternatives being compared.
- ② The cost should extend beyond the comparison of the drug acquisition costs and include the cost of the drug preparation and the storage when appropriate. Other costs to be evaluated may be the cost of physician, visits, numbers of hospital days and pharmacokinetic consultation. The least expensive agent, considering all these costs should be preferred.

CMA Process:

- ① 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.
- ② calculate pharmacy, nursing and physician cost, associated with the use of each medicine.
- ③ calculate laboratory cost associated with each medicine.
- ④ calculate cost of any other significant factors.
- ⑤ calculate and compare total medicine cost for each medicine.

Applications of CMA:

- ① cost saving of one program over another.
- ② applied in the formulary decision making when often the available evidence for a new product appears to be not better than the existing one.

Ex - ciprofloxacin tab 500 mg manufactured and marketed by different manufacturers can be subjected to CMA if the selected items were reported to have same benefits or outcomes for a specific infection.

- ③ Similarly if two or more brands of ciprofloxacin

Cost Benefit Analysis

Definition →

Cost benefit analysis compares the total cost of each alternative to resultant consequences or benefits of the intervention measured in monetary units.

This reflects the value of health status improvement and not cost of health care.

↳ It is easy to do the cost analysis of CBA. However, it is difficult and often controversial task to convert the benefits or outcomes into terms of money value. In CBA, the benefits are converted into the equivalent money units in the year in which they occur.

CBA type of pharmacoeconomic analysis is preferred by economists. However the employment on use of CBA in health care is always a problem. It is not an easy task to give monetary values to the clinical outcomes like relief of pain or improvement of quality of life.

CBA compares the total cost of each alternative to the outcomes future cost and outcomes are discounted or reduced to their current value. In programs and treatment alternatives where cost and benefits are not occurring simultaneously CBA can be used.

It can also be used while comparing programs with different objectives as all benefits are converted into money value. It may also discriminate against the unproductive population or the depended population.

Measurement of benefits:

Cost and benefit are considered to be either positive or negative. A cost can be incurred or avoided. A benefit can be gained or lost. Various approaches are suggested for the measurement of benefits in CBA. Benefits are measured using contingent valuation also commonly

referred to as willingness to pay method.

Willing to accept (WTA) is another method of contingent valuation. It is based on the minimum amount a patient or group of patients would accept or receive in order to be prepared to lose or avoid a service. None of the existing methods for measurement of benefits are perfect or ideal.

Steps in Conducting a CBA:

Step 1 → To identify clearly the intervention, Program, or therapeutic regimen to be evaluated.

Step 2 → To identify and value all of the resources consumed or costs of providing each intervention, program or regimen. Different types of resources should be recognised.

Step 3 → Benefits are identified.

Step 4 → To sum the value of all the cost and then sum all the benefits of Program, intervention or regimen. Total cost then may be subtracted from total benefits to determine net benefit.

$$\text{Net benefit} = \text{total benefit} - \text{total cost}$$

$$\text{Cost benefit ratio} = \text{total benefit} / \text{total cost}$$

- ① If the B/C ratio is > 1 then benefit exceed cost and program is socially valuable.
- ② If B/C ratio is $= 1$, the benefits equal the cost.
- ③ If the B/C ratio is < 1 , the program or the treatment alternative is not economically beneficial.

A program or treatment alternative with the highest net benefit or greatest benefit to cost ratio is considered as the best choice for positive clinical outcome.

Cost effectiveness Analysis

Introduction →

Cost-effectiveness analysis (CEA) is a way of summarizing the health benefits and resources used by competing healthcare programs so that policymakers can choose among them.

CEA involves comparing programs or treatment alternatives with different safety and efficacy profiles.

Cost is measured in dollar or rupees and outcomes are measured in terms of obtaining a specific therapeutic outcome.

These outcomes are often expressed in physical units, natural units or non rupee units (lives saved, life expectancy, or drop in blood pressure).

It can also be measured in terms of change in an intermediate clinical outcome like cost per night free of pain, night free of wheezing or percent change in blood cholesterol level.

The results of a CEA are expressed as cost/outcome for both therapies.

Thus, to compare the cost effectiveness of an H_2 receptor blocker and a proton pump inhibitor the cost per ulcer healed by each of the two drugs may be calculated and compared.

The results of CEA are also expressed as a ratio either as an average cost effectiveness ratio (ACER) or as an incremental cost-effectiveness ratio (ICER).

Average cost effectiveness ratio:

① An ACER represents the total cost of a program or treatment alternative divided by its clinical outcome to yield a ratio representing the rupee cost per specific clinical outcome.

gained, independent of comparisons. The ACER can be summarised as follows,

$$ACER = \frac{\text{Health care costs (monetary)}}{\text{Clinical outcome (not monetary)}}$$

Average cost effectiveness ratio →

- ① This allows the costs and outcomes to be reduced to a single value to allow for comparison.
- ② Using this ratio, the clinician would choose the alternative with the least cost per outcome gained.
- ③ The most cost effective alternative is not always the least costly alternative for obtaining a specific therapeutic objective.
- ④ In this regard, cost-effectiveness need not be cost reduction but rather cost optimization.

Incremental Cost effectiveness ratio (ICER)

often clinical effectiveness is gained at an increased cost.

Is the increased benefit worth the increased costs incremental CEA can be used to determine the additional cost and effectiveness gained when one treatment alternative is compared with the next best treatment alternative.

Thus instead of comparing the ACER of each treatment alternative, the additional cost that a treatment alternative imposes over another treatment is compared with the additional effect, benefit or outcome it provides

$$ICER = \frac{\text{Cost A (monetary)} - \text{Cost B (monetary)}}{\text{effect A (v.)} - \text{effect B (v.)}}$$

This formula yields the additional cost required to obtain the additional effect gained by switching from drug A ~~and~~ to drug B.

Handling of results in CEA:

Consider the four possible results of CEA:

① The new treatment is more effective and less expensive. The costs are lowest and the benefits are highest. Here the choice is clear without any ambiguity, it is the choice of preference recommended to be selected.

② The new treatment is more effective and more expensive that is the cost is high and the benefits are more. Here the ICER should be calculated.

③ A judgement has to be made whether the additional benefits are worth the extra costs of the new drug.

④ The new treatment is less effective and less expensive. Here we have to answer one question whether the extra benefits provided by the standard treatment justifies the additional costs of retaining it as a preferred treatment when the option of a new, cheaper but less effective drug exists.

Cost utility Analysis:

Definition →

A form of economic study design in which interventions which produce different consequences in terms of both quantity and quality of life are expressed as utilities. These are measure which comprise both length of life and subjective levels of well being. The best known utility measure is the quality adjusted life year or QALY.

QALY →

Quality-adjusted life years measure health as combination of the duration of life (HRQoL)

HRQoL is measured on a preference scale anchored at 1 and 0 (a quality of life as bad as dead)

Figure illustrates how QALYs can capture improvements in both life expectancy and QoL.

CUA: When is CUA appropriate →

Drummond et al. enumerated several circumstances where CUA may be the most appropriate analytic approach.

① When quality of life is the important outcome.

② When the intervention affects both morbidity and mortality and a combined unit of outcome is desired.

③ When the interventions being compared have a wide range of potential outcomes and there is a need to have a common unit of outcome for comparison.

Need for Health State Utility Assessment →

① Healthcare has different objectives.

Ex - A diabetologist's objective might be reduction in diabetic complications.

Oncologist's objective might be to keep their patients alive and may be satisfied with a short increase in survival time.

Primary care providers' objective is often focus on shortening the cycle of acute illnesses for which mortality is not an immediate concern.

② When mortality is studied, those who are

alive are statistically coded as 1.0 and those who are dead are statistically coded as 0.0.
Incremental cost utility ratio:

- It is also known as cost per QALY.
This is calculated as the difference in the expected cost of two interventions divided by the differences in the expected QALYs produced by the two interventions.

If treatment A provides on average an increase of 3.5 years life expectancy but that is valued at the utility of 0.9 then the health gain for this intervention is $0.9 \times 3.5 = 3.15$ QALY.

$$ICUR = \frac{CA - CB}{QALY_A - QALY_B}$$

$$QALY = \text{Utility} \times \text{Effectiveness}$$

Methods:

There are four common methods for deriving utility-like measures of health status or QALYs:

1. Health rating method → This derives health ratings from questionnaires with healthy, experts potential subjects of treatment, or members of society in general. Individuals are asked to assign values b/w 0 and 1 to various health states.

2. Time trade off method →

Respondents asked to compare different combinations of length and quality of life. The trade offs in the responses provide a basis for ranking various states.

Record linkage System:

Record-linkage is the systematic bringing together of the records of individuals in a large population. This is particularly important for medical records, as medical data arising from different health care contacts are usually stored separately.

By linking all the medical information about individuals in a population, even where this information originates in different data sources, all medical event can be considered together. In particular, they have made a significant contribution to pharmacovigilance, which involves linking drug exposure to outcomes data. Record-linkage has been facilitated in recent years by advances in computerization. Computerized record linkage has the advantages of quality control, speed, consistency, reproducibility of results and the ability to handle large volumes of data.

There are two methods by which the linkage of records belonging to the same individual but stored separately, can be achieved.

Deterministic linkage: refers to linkage that is based on the use of defined identifiers for each individual. These are usually assigned centrally and used in any records that are kept for that individual.

Probabilistic linkage: is based on combinations of non-unique characteristics of each individual, such as name, date of birth or gender.

These standard identifying items are prone to discrepancies due to errors or changes in status.

Therefore patterns of agreement and disagreement b/w identifying items are translated into quantitative scores, which are then used to predict whether the two records should be linked.

Record Linkage Systems: Components

The research databases are used to link files longitudinally at the individual level and are organized from the following components.

Membership data →

A member enrollment file stores demographic information, date of birth, gender, place and type of employment and benefit package, as well as linkage to dates of enrollment and disenrollment. A unique identifier is assigned to each member at the time of enrollment and is retained if a member disenrolls and later re-enrolls.

Medical claims:

A claim form must be submitted by a health care professional to receive payment for any covered service. Medical claims are collected from all health care sites (e.g. inpatients, hospital outpatient, emergency room, surgery centre, physician office).

Pharmacy claims:

Claims for covered pharmacy services typically are submitted electronically by the pharmacy at the time a prescription is filled. The claims history is a profile of all prescription drugs covered by the health plan and filled by the member. Each claim specifies code, drug name, date dispensed, dosage of medication - dispensed, duration of the prescription in days and quantity dispensed.

Health professional data:

A separate file contains data on the health plan's participating physicians and other health professionals. A unique number is assigned to each health professional and institution. Precautions are taken to protect the identity of health

health professionals

Strengths →

The research databases provide an efficient method to identify and study exposures to prescription drugs and biologics.

Further, drug or biologic utilization and potential adverse events identified within the plans reflect usual practice within the general medical community.

Whereas clinical trials for new drugs are typically conducted in university or other unique settings to determine efficacy, post marketing surveillance enables researchers to determine the effectiveness when usage has diffused to the broader medical community.

Weaknesses:

A limitation of claims data with respect to characterizing exposure to drug is a lack of information on patient adherence with the therapeutic regimen.

If reimbursement to a specialist is capitated and there is no requirement to submit a bill for payment that service may not be included as part of the databases.

Another limitation is the length of time required to obtain all claims for a given time frame the claims lag is short for pharmacy claims (1 month) but longer for physician and facility claims (78 months)

Applications:

- ① Record linkage is an important tool in creating data required for examining the health of public and of the health care system itself. It can be used to improve data

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holding, data collection quality assessment and the dissemination of information.

① Data sources can be examined to eliminate duplicate records, to identify underreporting and missing cases to create person-oriented health statistics and to generate disease registries and health surveillance system, some cancer registries link various data sources (pathology and clinical reports, and death registrations) to generate their registries).

② Record linkage is also used to create health indicators for eg fetal and infant mortality is general indicator of a country's socioeconomic development, public health and maternal and child services. If infant records are matched to birth records, it is possible to use birth variables, such as birth weight and gestational age, along with mortality such as ~~ca~~ cause of death, in analysing the data.

Linkage can also help in follow-up studies of cohort or other group to determine factors such as vital status, residential status on health outcomes. Tracing is often needed for follow-up of industrial cohort, clinical trials and longitudinal surveys to obtain the cause of death and/or cancer.

Bias:

Bias refers to the tendency of a measurement process to over or under estimate the value of a population parameter.

Introduction:

Bias refers to an error which causes an estimate of a parameter to differ in a systematic way from the true value.

The presence of bias causes a study to yield incorrect results.

Bias can occur in case control studies, cohort studies or observational studies.

⊛ Three types are there →

1. Selection bias
2. Information bias
3. Confounding.

1. Selection Bias:

It refers to errors arising because the estimated exposure effect among subjects included in the study differs from that ~~as~~ which would have been obtained from including the entire study base.

Selection bias is a problem in clinical studies which are not ~~are~~ randomised.

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It is a distortion of the measurement of an estimate of effect, which is due to the selection into the study groups of subjects who have an unusual and unequal relationship between drug exposure and outcome.

- a. referral bias.
- b. self-selection bias.
- c. prevalence study bias.
- d. protopathic bias.

a) Referral bias: Can occur if the reasons for referring a patient to the hospital for instance are related to the drug exposure status, eg - when the use of the drug contributes to the diagnostic process. This is a particular problem when an illness presents in a manner such that an accurate diagnosis is not always obtained.

b) Self-Selection bias: May occur when study participants themselves decide to participate or to leave a study based on both drug exposure and change in health status. Hence, the association observed in the study sample may not be representative of the real association in the source population. This problem is particularly important in case-control studies or historical cohort studies, because both outcome and exposure are already manifest when study subjects are recruited.

c) Prevalence bias: is another type of selection bias that may occur in case-control studies when prevalent cases rather than new cases of a condition are selected for a study. Since prevalence is proportional to both incidence and duration of the disease, an association with prevalence may be related to the duration of the disease rather than to its incidence.

1) Protopathic bias: It is a term that was first used by Feinstein. It may occur if a particular treatment on exposure was started, stopped or otherwise changed because of the baseline manifestation caused by a disease on other outcome event.

2. Information Bias:

It arises from inaccuracies in the information collected on subjects in the study, resulting in misclassification of exposures, outcomes or covariates.

Eg - patient recall of previous drug exposures has been shown to be subject to error with the extent of inaccuracy differing by medication type, duration of therapy, recall interval and patient age.

Recall bias → is an important concern in retrospective studies eg in case-control studies. Cases and controls may have a selective memory of their past exposures. In studies of birth defects for example, mothers with an impaired child may give a more valid and complete report of their exposure to drugs during pregnancy as a result of devoting more time to contemplating the cause of the birth defect.

Detection bias:

Can affect either cohort or case control studies. It occurs in case-control studies when the procedures for exposure assessment are not similar in cases and control. In cohort studies, it occurs when the follow-up procedures for detecting adverse events differ according to the exposure status of the participants.

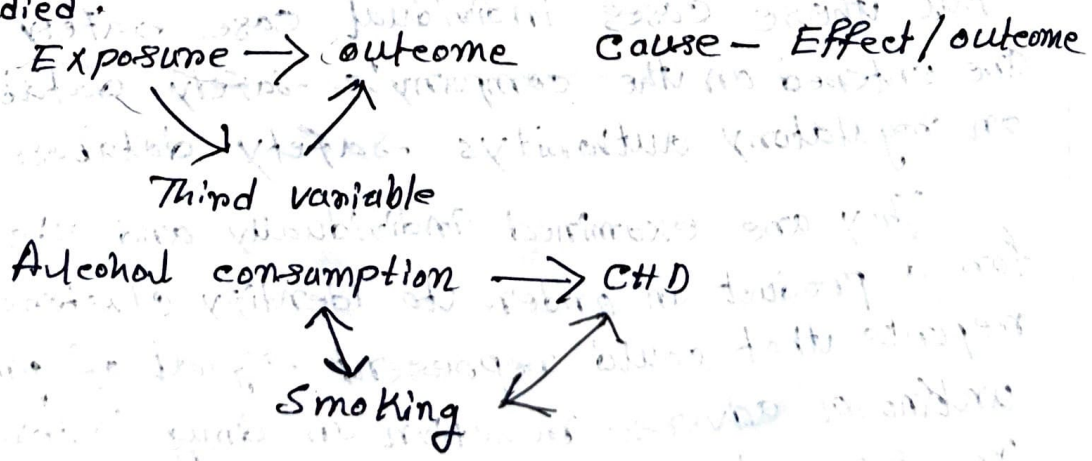
For instance, women taking postmenopausal hormonal supplements are likely to see their doctors more often than other women. These women are therefore more likely to be examined for breast or endometrial cancer, or for the risk of cardiovascular disease. This differential follow-up may lead to an excess number of diagnosed diseases in the treated group and a falsely elevated risk.

3. Confounding Bias:

Confounding occurs when the estimate of a measure of association between drug exposure and death status is distorted by the effect of one or more variables that are also risk factors for the outcome of interest.

Here exposure groups differ with respect to an extraneous factors related to the outcome, the indirect association is called the confounded association. A confounder is a factor that is associated with the outcome of the study if this factor is not properly considered and adjusted, the result will be changed dramatically leading to erroneous study conclusion.

When another exposure exists in the study population (besides the one being studied) and is associated both with disease and the exposure being studied.



TERATOLOGY

- Teratology is the science that studies the causes, mechanisms, and patterns of abnormal development.
- Developmental disorders present at birth are called congenital anomalies, birth defect or congenital malformation.
- Congenital anomalies are of four clinically significant types: malformation, disruption, deformation and dysplasia.

BIRTH DEFECTS

- 3% of all live-born infants have a major anomaly.
- Additional anomalies are detected during postnatal live — about 6% at 2 year-olds, 8% in 5year-olds, other 2% later.
- Single minor anomalies are present in about 14% of newborns.
- Major anomalies are more common in early embryos (up to 15%) than they are in newborns (3%). Most severely malformed embryos are spontaneously aborted during first 6 to 8 weeks.

Teratology - terms

- **Malformation** is a primary structural defect resulting from a localized error of morphogenesis.
- **Disruption** is specific abnormality that results from disruption of normal developmental processes. It depends on time not on agent.
- **Deformation** is an alteration in shape / structure of previously normally formed part.
- **Syndrome** is a recognized pattern of malformations with a given etiology.

FACTORS THAT INFLUENCE TERATOGENICITY

- Nature of the agent.
- Dose

- Route
- Frequency of exposure
- Duration of exposure
- Gestational timing
- Concurrent exposures
- Concurrent illness
- Genetic susceptibility
 - Mother
 - Fetus

PRINCIPAL MECHANISMS OF TERATOGENESIS

- Cell growth or proliferation.
- Cell death.
- Cell migration.
- Cell and tissue interactions.
- Disruptions.

Mutagenesis:

- Principal mechanisms.
 - Gene mutation.
 - Chromosomal abnormalities.
- Before or after conception.
- Males and females both affected.

Anomalies caused by genetic factors

- Chromosomal aberrations are common and are present in 6 to 7% of zygotes — (Result = abort).
- Numerical chromosomal abnormalities —usually non-disjunction- error in cell division Down syndrome (21) Edwards (18) Patau (13) Turner (XO), Klinefelter (XXY).

- Structural chromosomal abnormalities —chromosome breaks = translocation, deletion (cri du chat syndrome), duplication, inversion.
- Mutant genes — achondroplasia, fragile-X syndrome.

Anomalies caused by environmental factors

- Teratogens are exogenous agents that may cause developmental defects:
- Drugs (warfarin, valproic acid, phenytoin, vitamin A, thalidomide, cytostatic drugs - cyclophosphamide, lithium carbonate).
- Chemicals (PCBs, methyl mercury, alcohols).
- Infections (rubella, cytomegalovirus, herpes, toxoplasma, syphilis).
- Ionizing radiation (RTG).
- Maternal factors (diabetes mellitus, hyperthermia, phenyl-ketonia, hyper-/hypothyroidism).

BASIC PRINCIPLES IN TERATOGENESIS

- Critical periods of development.
- Dosage of the drug or chemical.
- Genotype (genetic constitution) of the embryo and mother.

TERATOGEN

- Teratogenesis is process with threshold-level effect.
- Every chemical substance may be teratogenic. This effect depends on quantity. In small amount is without any effect.
- Teratogen is factor that is present in environment in so high amount that it can increase occurrence of embryo toxicity manifestation up to basic frequency in non-exposed population.
- Teratogenicity is a manifestation of developmental toxicity representing a particular case of embryo/fetotoxicity, by the induction or the increase of frequency of structural disorders in the progeny.

TESTING FOR TERATOGENICITY

- Standardized procedures for testing drugs for teratogenic potential are used.
- They use at least 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 highest 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 obviously applied to social drugs like tobacco, alcohol and addictive drugs.

PREGNANCY RISK CATEGORIES RESPONSE

- Labeling of some prescription drugs includes information about the level of risk for the fetus and the extent of caution necessary in their use. The FDA has established five categories (A, B, C, D, and X) to indicate a drug's potential for causing teratogenicity. This format was first announced in the September 1979 FDA Drug Bulletin. Because of labeling revisions, many products now use this format.
- A similar, but somewhat expanded, classification system was adopted by the Australian Drug Evaluation Committee (ADEC) in 1989. Germany set forth its own classification system.

US FDA PREGNANCY CATEGORY DEFINITIONS

- A** - Adequate, well-controlled studies in pregnant women fail to demonstrate a risk to the fetus in the first (second, third, or all) trimester(s), and the possibility of fetal harm appears remote.
- B** - Animal studies do not indicate a risk to the fetus; however, there are no adequate, well-controlled studies in pregnant women. OR Animal studies have shown an adverse effect

on the fetus but adequate, well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus. Despite the animal findings, the possibility of fetal harm appears remote, if used during pregnancy.

- C - Animal studies have shown that the drug exerts teratogenic or embryocidal effects, and there are no adequate, well-controlled studies in pregnant women, OR No studies are available in either animals or pregnant women.
- D - Positive evidence of human fetal risk exists, but benefits in certain situations (eg, life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.
- X - Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant.

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?
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- 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 drugs. 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?

Ad hoc data sources:

Introduction:

The term Ad hoc data refers to the billion of ~~byte~~ bytes of non-standard and continuously evolving data spread across all computer systems.

Such data includes server logs, distributed system performance, telephone records, financial data. An ad hoc data source is any semi-structured data source for which useful data analysis and transformation tools are not readily available.

The data that constitutes a single, abstract, source often comes from many different, concrete, physical destinations distributed across the internet.

Managing Ad Hoc data is a bone of the implementers of distributed systems. These system may have hundreds or thousands of

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• heterogeneous distributed component, keeping these components running smoothly is a continuous maintenance task of significant complexity.

① Consequently, each component is a well-designed distributed system produces a continuous stream of log files that measure its performance and health.

Eg → distributed Ad Hoc data sources.

Ad Hoc case-control studies:

Case-control studies can be performed as Ad Hoc studies as well cases can then be recruited from whatever source is appropriate for that disease, whether hospitals outpatient practices or some other source. Investigation in some geographic areas maintain ongoing relationships with a number of hospitals to permit case finding for case-control studies.

Case definitions must be clear. Cases should be incident cases that is individuals who have recently developed the disease, so one can inquire about exposures that precedes the onset of the disease. All individuals who meet the case definition should be enrolled if possible to decrease the risk of a selection bias.

Controls can then be recruited from either the site of medical care for the cases or from the community where the cases come from.

Community controls can be recruited from friends of the cases from neighbors of the cases, from a reverse telephone directory, by using random digit dialing or from some comprehensive listing of the target population.

A list, organized medical care programs which can provide listings of eligible individuals such as general practitioners and other special

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Situations.

- ① An example would be a study limited to the elderly which could obtain listing of those eligible for medicare in the local area.
- ② Ad Hoc cohort studies can be useful to study new drugs, but are expensive and large and need to have a concurrent control group to avoid attributing all adverse events to the drug.
- ③ Ad Hoc studies can be whatever size the researcher desires for the study at hand.
- ④ Historically, Ad Hoc epidemiologic studies have been employed to assess potential vaccine adverse events. Newer projects based on a automated

Studies of vaccine safety

Vaccines are immunobiological substances designed to produce specific protection against an other immune mechanisms.

The vaccine mimics infection with the respective pathogen but without risk of the disease.

The goal of all vaccines is to promote a primary immune reaction so that when the organism is again exposed to the antigen a much stronger secondary immune response will be elicited. No vaccine is perfectly safe or effective, however and concerning even adverse events (AEs) after immunizations have often threatened the stability of immunization programs.

Type of vaccines:

- ① Live (attenuated)
- ② Inactivated (Killed)
- ③ Toxoids.
- ④ Subunit and recombinant

Adverse event following immunization:

AEFI is a medical incident that takes place after immunization causes concern and is believed to be caused by immunization, can be either true adverse event such really a result of the vaccine or immunization or coincidental events that are not due to vaccine or immunization process.

Clinical problems to be addressed by pharmacovigilance research:

The tolerance for ~~adverse~~ adverse reactions to vaccines given to healthy persons - especially healthy babies is lower than to products administered to persons already sick or higher.

(83)

Standard of safety is required for vaccines because of the large number of persons who are exposed some of whom are compelled to do so by law on regulation for public health reasons. These issues lead often to a need to investigate much more adverse events following vaccinations than for unlike many classes of drugs for which other effective therapy may be substituted. Vaccines generally have few alternative choices and the to withdraw a vaccine may have wide ramifications.

Establishing associations of adverse events with vaccines and prompt definition of the attributable risk are critical in placing adverse events in the proper risk / benefit perspective.

By virtue of vaccines being relatively universal exposures, despite the relative rarity of serious true vaccine reactions, the absolute number of clinically significant vaccine adverse event reports received annually in the US now averages ~15000.

Research in vaccine safety can help to distinguish true vaccine reactions from coincidental events, estimate their attributable risk, identify risk factors that may permit development of valid contraindications and if the pathophysiologic mechanism becomes known, develop safer vaccines.

Methodologic problems to be addressed by pharmaco-epidemiologic Research →

An Institute of medicine (IOM) review of vaccine safety found that the US knowledge and ~~research~~ research capacity has been limited by.

- i) inadequate understanding of biologic mechanisms underlying adverse events.
- ii) insufficient or inconsistent information from case reports and case series.
- iii) inadequate size or length of follow-up of many population based epidemiologic studies.

- iv) limitations of existing surveillance systems to provide persuasive evidence of causation and,
- v) Few experimental studies published relative to the total number of epidemiologic studies published.

In ensuing attempts to overcome these limitations, epidemiology has been vital in providing the scientific methodology for assessing the safety of vaccines.

Methodologic problems:

Epidemiology has been vital in providing the scientific methodology for assessing the safety of vaccines,

- Signal detection.
- Assessment of causality.
- Measurement accuracy.
- confounding and bias.
- Sample size.

Signal Detection:

High profile vaccine adverse events, such as intussusception following Rotavirus vaccination demonstrate the need for surveillance systems able to detect potential aberrations in a timely manner. Some factors make identification of true signals difficult though even, for example, many vaccines are administered early in life, at a time when the baseline risk is constantly evolving. Until the recent advent of systematic analyses of automated data and data mining of spontaneous reports methods, detection of vaccine safety signal occurred as much due to a persistent patient as from data analysis.

Assessment of causality:

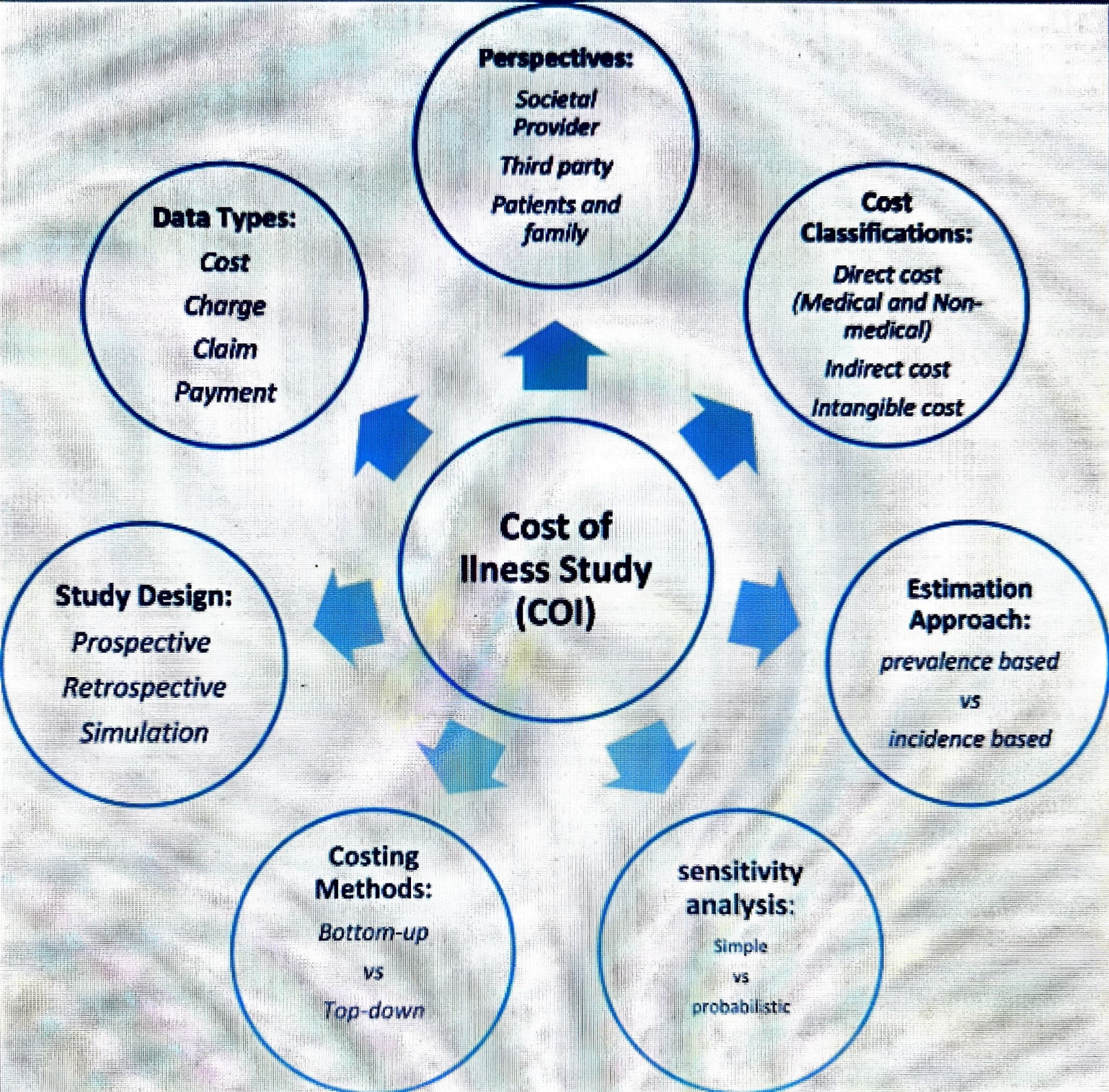
Assessing whether any adverse events was actually caused by vaccine is generally not possible unless a vaccine specific clinical syndrome myopenicanditis in healthy young adult recipient of small pox vaccine, recurrence upon rechallenge or a vaccine-specific laboratory finding like mumps vaccine virus isolation can be identified when the adverse event also occurs in the absence of vaccination. epidemiologic studies are necessary to assess whether vaccinated persons are at higher risk than unvaccinated persons.

Measurement Accuracy:

Misclassification of exposure status may occur if there is poor documentation of vaccinations. Documentation of exposure status has been fairly good through school age, but difficulty has been encountered in ascertaining vaccination status in older persons.

Sample Size:

Because outcome events are often extremely rare, it may be a challenge to identify enough cases for a meaningful study. The difficulty with adequate study power is further compounded in assessing rare events in populations less frequently exposed. Subpopulations with special indications. For studies of rare outcomes, case-control designs are the most efficient. Such studies typically sample the source population of cases identify appropriate control group, and assess the exposure status of both groups to estimate the risk associated with exposure.



Factors
determination.

Costs in COI

- A comprehensive cost of illness study includes both direct and indirect costs.
- Direct costs measure the opportunity cost of resources used for treating a particular illness.
- Indirect costs measure the value of resources lost due to a particular illness.

Indirect cost:

- There are three primary approaches to estimate indirect cost:
- The human capital method
- The friction cost method

- The willingness to pay method

Human capital method

- For practically the human capital method is generally recommended.
- The human capital method measures the lost production in terms of lost earning, of a patient or caregiver.
- For mortality or permanent disability costs, the approach multiplies the earnings lost at each age by the probability of living to that age.

Friction cost method

- A related method, the friction cost method, measures only the production losses during the time it takes to replace a worker.
- This approach assumes that short-term work losses can be made up by an employee and the loss of employee only result in costs in the time it takes a new employee to be hired and trained, known as the friction period.

Willingness to pay method

- The willingness to pay approach measures the amount an individual would pay to reduce the probability of illness or mortality.
- There are various methods of determining an individual's willingness to pay, including surveys, examining the demand for products that lead to greater health or safety, and other related methods.

Direct costs

- Direct costs can be estimated using one of three approaches:
- The top-down approach
- Bottom – up approach
- The econometric approach

Top-down approach

- The top – down approach also known as the epidemiological or attributable risk approach.
- Measures the proportion of a disease that is due to exposure to the disease or risk factor.
- The approach uses aggregated data along with a population – attributable fraction to calculate the attributable costs.
- In this the proportion of medical care for disease B attributable to disease A is measured as follows:
- $PAF = p(RR - 1) / [p(RR - 1) + 1]$
- Where P is the prevalence rate of disease A and
- RR is the unadjusted relative risk of disease B
- For people with disease A, compared with those without disease A.

Bottom-Up approach

- While the top-down approach is a valid approach, to avoid the need to calculate PAFs and the potentially more cumbersome methods needed to prevent a bias in the estimate, the bottom up or econometric approach can be used.
- The bottom - up approach estimates costs by calculating the average cost of treatment of illness and multiplying it by the prevalence of the illness.
- The bottom up approach often multiplies the unit cost of a particular treatment by the average amount of utilization of the treatment to get an average cost estimate of the treatment.

Econometric approach

- The econometric or incremental approach estimates the difference in costs between a cohort of the population with the disease and a cohort of the population without the disease.
- The two cohorts are matched, usually via regression analysis by various demographic characteristics (e.g. sex, age, race) and the presence of other chronic condition.
- The econometric approach measures the incremental difference between persons who have the disease and those who do not, it often only requires one dataset.

Introduction



- Confounder (also confounding variable, confounding factor, or lurking variable) is a variable that influences both the dependent variable and independent variable, causing a spurious association.
- Confounding is a causal concept, and as such, cannot be described in terms of correlations or associations.
- When a non-casual association is observed between a given exposure and outcome is as a result of the influence of a third variable, it is termed confounding, with the third variable termed a confounding variable.
- A confounding variable is causally associated with the outcome of interest, and *non-causally or causally associated with the exposure*, but is not an intermediate variable in the causal pathway between exposure and outcome (Szklo & Nieto, 2007).

There are three conditions that must be present for confounding to occur

- The confounding factor must be associated with both the risk factor of interest and the outcome.
- The confounding factor must be distributed unequally among the groups being compared.
- A confounder cannot be an intermediary step in the causal pathway from the exposure of interest to the outcome of interest.

Controlling of confounding

- **Case-control studies** : Assign confounders to both groups, cases and controls, equally.
- **Cohort studies**: A degree of matching is also possible and it is often done by only admitting certain age groups or a certain sex into the study population, creating a cohort of people who share similar characteristics and thus all cohorts are comparable in regard to the possible confounding variable.
- **Double blinding**: Conceals from the trial population and the observers the experiment group membership of the participants.

Controlling of confounding



- **Randomized controlled trial:** The study population is divided randomly in order to mitigate the chances of self-selection by participants or bias by the study designers.
- **Stratification:** for small number of confounders.

Types



- **Operational confounding:** Occur in both experimental and non-experimental research designs. This type of confounding occurs when a measure designed to assess a particular construct inadvertently measures something else as well.
- **Procedural confounding:** Occur in a laboratory experiment or a quasi-experiment. This type of confound occurs when the researcher mistakenly allows another variable to change along with the manipulated independent variable.
- **Person confounding:** Occurs when two or more groups of units are analyzed together (e.g., workers from different occupations), despite varying according to one or more other (observed or unobserved) characteristics (e.g., gender).

Effects of Confounding



- May cause an overestimate of the true association (positive confounding) or an underestimate of the association (negative confounding).



Method Favored by Biostatisticians

$$\text{Magnitude of confounding} = \frac{RR_{\text{crude}} - RR_{\text{adjusted}}}{RR_{\text{crude}}}$$

Method Favored by Epidemiologists

$$\text{Magnitude of confounding} = \frac{RR_{\text{crude}} - RR_{\text{adjusted}}}{RR_{\text{adjusted}}}$$

Markov Model

A stochastic model describing a sequence of possible events in which the probability of each event depends only on the state attained in the previous event.

Markov chain:

Named after Andrey Markov, are a mathematical tool for statistical modeling.

They play a central role in information sciences among other areas and are an important tool in modern applied mathematics.

① It is a way to represent a changing set of health states over time, where there is a known probability or rate of transition from one health state to another.

① It is a statistical representation of recurrent events over time that can be incorporated into decision analysis.

① Markov models are useful when a decision problem involves risk that is continuous over time when the timing of events is important and when important events may happen more than once.

① Markov model assume that a patient is always in one of finite number of discrete health states called Markov states.

Types Markov process:

Markov processes are categorized according to whether the state-transition probabilities are constant over time or not.

In the most general type of Markov process the transition probabilities may change over time.

The first component is the probability of dying from ~~unrelated~~ unrelated causes. In general, this probability changes over time because, as

the patient gets older, the probability of dying from unrelated causes will increase continuously.

- ② The second component is the probability of suffering a fatal hemorrhage or embolus during the cycle. This may or may not be constant over time.
- ③ All events are represented as transitions from one state to another.
- ④ A Markov model may be evaluated by matrix algebra, as a cohort simulation or as a Monte Carlo simulation.
- ⑤ A newer representation of Markov models, the Markov-cycle tree, uses a tree representation of clinical events and may be evaluated either as a cohort simulation or as a Monte Carlo simulation.
- ⑥ The ability of the Markov model to represent repetitive events and the time dependence of both probabilities and utilities allows for more accurate representation of clinical setting that involve these issues.
- ⑦ In traditional decision tree the terminal nodes are all single outcomes.
- ⑧ When models must consider events that occur over time or events that may recur in time, the traditional branch and node structure is an inefficient method for presenting this events.

Strengths And Weakness Medicaid and Medicare

Strengths

- 1) Clinical validity.
- 2) Validity of Demographic Information
- 3) Population coverage.
- 4) Large population base.
- 5) Cost effective to use.

Weakness

- 1) Record of Care Received.
- 2) Diagnosis code does not provide enough detail.
- 3) Different care settings use different coding systems for procedures.
- 4) limited clinical information.

Meta-analysis would be used for the following purposes:

To establish statistical significance with studies that have 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 that are not statistically significant

QALY →

Quality-adjusted life years measure health as combination of the duration of life (HRQoL)

HRQoL is measured on a preference scale anchored at 1 and 0 (a quality of life as bad as dead)

Figure illustrates how QALYs can capture improvements in both life expectancy and QoL.

QOL - This approach incorporates both increases in survival time and changes in quality of life into one measure. An increased quality of life (QoL) is expressed as a utility value on a scale of 0 (dead) to one (perfect quality of life).

VAERS is the nation's early warning system that monitors the safety of vaccines after they are authorized or licensed for use by the U.S. Food and Drug Administration (FDA). VAERS is part of the larger vaccine safety system in the United States that helps make sure vaccines are safe. The system is co-managed by CDC and FDA.

VAERS accepts and analyzes reports of possible health problems—also called “adverse events”—after vaccination. As an early warning system, VAERS cannot prove that a vaccine caused a problem. Specifically, a report to VAERS does not mean that a vaccine caused an adverse event. But VAERS can give CDC and FDA important information. If it looks as though a vaccine might be causing a problem, FDA and CDC will investigate further and take action if needed.

The important criteria for pharmacoeconomics study are as follows :

- ① Study objective.
- ② Study perspective.
- ③ Pharmacoeconomics method.
- ④ Study design.
- ⑤ Choice of intervention.
- ⑥ Cost and consequences.
- ⑦ Discounting.
- ⑧ Study results.
- ⑨ Sensitivity analysis.
- ⑩ Study conclusion.
- ⑪ Sponsorship and bias.
- ⑫ Use of comparator.

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Uses of the literature.

it is use ->

- ① As an aid in clinical decision making.
- ② In understanding the potential effect of therapy.
- ③ In understanding the transition from efficacy to efficiency in clinical practice.
- ④ To evaluate, interpret and transfer the results to other health care setting and countries.

B	C	D
Brand-Names	Product-Description	Recall-Reason-Description
Golden State Medical Supply, Incorporated	Clopidogrel 75mg Tablets, Atenolol 25mg Tablets	Due to Label Mix-up
Exela & Civica	Sodium Bicarbonate Injection, USP, 8.4%, 50 mEq/50 mL vial	Vial Breakage
Aurobindo Pharma USA, Inc.	Quinapril and Hydrochlorothiazide Tablets USP, 20mg / 12.5mg, 90's HDPE bottle	Due to presence of Nitrosamine Drug Substance Related Impurity (NDSRI), N-Nitroso-Quinapril
Adam's Polishes	Hand sanitizer	Presence of methanol
Exela	Sodium Bicarbonate Injection, USP, 8.4%, 50 mEq/50 mL vial	Vial Breakage
Fagron	SyrSpend SF 500mL and 4L	Potential contamination with Burkholderia gladioli
Teva	Anagrelide Capsules	Dissolution Test Failure
Artri Ajo King	Joint supplements	Contains diclofenac
Allergy Bee Gone for Kids	Nasal Swab Remedy	Product contains elevated levels of Bacillus cereus
Major Arti King	Milk of Magnesia, Magnisium Hydroxide/Aluminum Hydroxide/Simethicone Oral Suspension	 Due to microbial contamination
CVS Health	Artri King Reforzado con Ortiga y Omega 3 Magnesium Citrate Saline Laxative Oral Solution, Lemon Flavor	Undeclared Diclofenac and Dexamethasone
Launch Sequence	Launch Sequence Aphrodisia and Euphoria Capsules	Microbial contamination with Gluconacetobacter liquefaciens
	Insulin Glargine (Insulin glargine-vfan) Injection	Contain Tadalafil