

• Causal association:

- A noxious agent is said to have a causal association with a particular disease when it can be shown that it plays some role in producing the occurrence of the disease.

PHARMACOEPIDEMIOLOGICAL METHODS

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CRITERIA FOR THE CAUSAL NATURE OF AN ASSOCIATION:

- The "Criteria for the causal nature of an association" were first put forth by Sir Austin Bradford Hill in 1965.
- The best known description of them was in the US Public Health Service's first Surgeon General's Report on Smoking and Health, published in 1964.
- No one of them is absolutely necessary for an association to be a causal association. Analogously, no one of them is sufficient for an association to be considered a causal association. Essentially, the more criteria that are present, the more likely it is that an association is a causal association. The fewer criteria that are met, the less likely it is that an association is a causal association.

Table : Criteria for the causal nature of an association

- (1) Coherence with existing information (biological plausibility)
- (2) Consistency of the association
- (3) Time sequence
- (4) Specificity of the association
- (5) Strength of the association
 - (a) Quantitative strength
 - (b) Dose-response relationship
 - (c) Study design

1. Coherence with existing information (biological plausibility):

- Coherence with existing information or biological plausibility (This refers to whether the association makes sense, in light of other types of information available in the literature, which include data from other human studies, data from studies of other related questions, data from animal studies, or data from *in vitro* studies, as well as scientific or pathophysiologic theory.)
- Example : the association between cigarettes and lung cancer, cigarette smoke is a known carcinogen, based on animal data. In humans, it is known to cause cancers of the head

Specificity of the association:

1- the uniqueness of a relationship b/w a causal factor and the occurrence of a disease.

2- Association is specific when a certain exposure is associated with only one disease.

and neck, the pancreas, and the bladder. Cigarette smoke also goes down into the lungs, directly exposing the tissues in question.

- Thus, it certainly is biologically plausible that cigarettes could cause lung cancer. It is much more reassuring if an association found in a particular study makes sense, based on previously available information, and this makes one more comfortable that it might be a causal association.
→ acceptable to the mind

2. Consistency of the association:

- The second criterion listed is the consistency of the association. A hallmark of science is reproducibility: if a finding is real, one should be able to reproduce it in a different setting. This could include different geographic settings, different study designs, different populations, etc.
- Example: In the case of cigarettes and lung cancer, the association has now been reproduced in many different studies, in different geographic locations, using different study designs. The need for reproducibility is to an error committed in the study, which is not apparent to either the investigator or the reader.

3. Time sequence:

- The third criterion listed is that of time sequence—a cause must precede an effect.
happen before
come before
- Although this may seem obvious, there are study designs from which this cannot be determined.
- Example: if one were to perform a survey in a classroom of 200 medical students, asking each if he or she were currently taking diazepam and also whether he or she were anxious, one would find a strong association between the use of diazepam and anxiety, but this does not mean that diazepam causes anxiety!
- in the example of cigarettes and lung cancer, obviously the cigarette smoking usually precedes the lung cancer, as a patient would not survive long enough to smoke much if the opposite were the case.

4. Specificity of the association:

- The fourth criterion listed is specificity (This refers to the question of whether the cause ever occurs without the presumed effect and whether the effect ever occurs without the presumed cause.)
Presume: presumed
- This criterion is (almost never met in biology) with the occasional exception of infectious diseases.

- Measles never occurs without the measles virus, but even in this example, not everyone who becomes infected with the measles virus develops clinical measles.}}
- Certainly, not everyone who smokes develops lung cancer, and not everyone who develops lung cancer was a smoker.
- Some authors even omit this as a criterion, as it is so rarely met. When it is met, however, it provides extremely strong support for a conclusion that an association is causal.

5. Strength of the association:

- The fifth criterion listed is the *strength of the association*. (This includes three concepts: its quantitative strength, dose-response, and the study design.

a) Quantitative strength:

- The *quantitative strength of an association refers to the effect size*. To evaluate this, one asks whether the magnitude of the observed difference between the two study groups is large.
- A quantitatively large association can only be created by a causal association or a large error, which should be apparent in evaluating the methodology of a study.
- A quantitatively small association may still be causal, but it could be created by a subtle error, which would not be apparent in evaluating the study.
- Conventionally, epidemiologists consider an association with a relative risk of less than 2.0 a weak association.
- Certainly, the association between cigarette smoking and lung cancer is a strong association: studies show relative risks ranging between 10.0 and 30.0.

b) Dose-response relationship:

- A dose-response relationship is an extremely important and commonly used concept in clinical pharmacology and is used similarly in epidemiology.
- (A dose-response relationship exists when an increase in the intensity of an exposure results in an increased risk of the disease under study.
- Equivalent to this is a duration-response relationship, which exists when a longer exposure causes an increased risk of the disease.
- The presence of either a dose-response relationship or a duration-response relationship strongly implies that an association is, in fact, a causal association.

- Certainly in the example of cigarette smoking and lung cancer, it has been shown repeatedly that an increase in either the number of cigarettes smoked each day or in the number of years of smoking increases the risk of developing lung cancer.

c) Study design

- Study design refers to two concepts: whether the study was well designed, and which study design was used in the studies in question.
- The former refers to whether the study was subject to one of the three errors, namely random error, bias, and confounding. Table on the next slide presents the study designs typically used for epidemiologic studies, or in fact for any clinical studies.
- Associations shown by studies using designs at the top of the list are more likely to be causal associations than associations shown by studies using designs at the bottom of the list.

Table : Advantages and disadvantages of epidemiologic study designs

Study Design	Advantages	Disadvantages
Randomized clinical trial (Experimental study)	Most convincing design Only design which controls for unknown or unmeasurable confounders	Most expensive Artificial Logistically most difficult Ethical objections
Cohort study	Can study multiple outcomes Can study uncommon exposures Selection bias less likely Unbiased exposure data Incidence data available	Possibly biased outcome data More expensive If done prospectively, may take years to complete
Case-control study	Can study multiple exposures Can study uncommon diseases Logistically easier and faster Less expensive	Control selection problematic Possibly biased exposure data
Analyses of secular trends Case series	Can provide rapid answers Easy quantitation of incidence	No control of confounding No control group, so cannot be used for hypothesis testing
Case reports	Cheap and easy method for generating hypotheses	Cannot be used for hypothesis testing

Study Designs in Pharmacoepidemiology

Study Design:

• A study design is a specific plan or protocol for conducting the study, which allows the investigator to translate the conceptual hypothesis into an operational one.

• Pharmacoepidemiological studies are mostly observational, they attempt to measure effects under real-life conditions. Larger populations can be studied than in clinical trials and the findings are likely to be generally applicable. However, without randomisation, attribution of causation is more difficult. Observational studies provide evidence of association (or no association) and a judgement then has to be made on causation taking into account all the available information.

Four possible explanations for a positive association have to be considered:

- Chance (taking into account the level of statistical significance)
- Bias (a systemic measurement error)

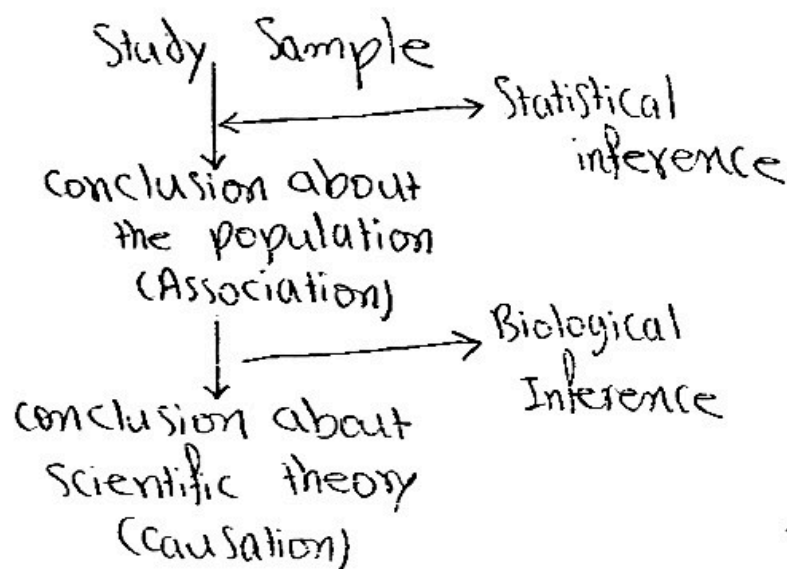
- Confounding (the association is produced by a third factor which is related to both drug use and outcome)
- Causal effect (if the other explanations can reasonably be excluded).

Study design- "Scientific method"

It is a three step procedure:

- 1- One selects a group of subjects for study
- 2- One uses the information obtained in this sample of study subjects to generalise and draw conclusion about the population in general
- 3- One generalises again, drawing a conclusion about scientific theory or causation.

Overview of scientific method:



Example:

- A randomised clinical trial of the efficacy of Enalapril in lowering blood pressure.
- 40 subjects (20/20 - Enalapril/placebo)
- 40 mid age hypertensive patients are selected as subjects, these are the study sample, and these subjects are divided in two groups of 20 subjects in one group. Now one group is given Enalapril and another group is given a placebo. So the expected results is group who is receiving Enalapril will show decrease in blood pressure and no change of blood pressure in the group receiving placebo, but if the result in this experiment is opposite then the study is scrapped and not further proceeded. خبر انقضی

• Types of studies and Advantages /Disadvantages

1) Randomized Clinical trial (Experimental Study)	→ Most convincing design • Only design which controls for unknown or unmeasurable confounders	• Most expensive • Artificial • Logistically most difficult • Ethical Objections
Cohort Studies	• Can study multiple outcomes • Can study uncommon exposures • Selection bias less likely • Unbiased exposure data • Incidence data available	• Possibly biased outcome data • More expensive • If done prospectively, may take years to complete
Case- control study	• Can study multiple exposures • Can study uncommon diseases • Logistically easier & faster • Less expensive	• Control selection problematic • Possibly biased exposure data
Analyses of secular trends	• Can provide rapid answer	* No control of confounding
Case series	• Easy quantitation of incidence	• No control group so cannot be used for hypothesis testing
Case Reports	• Cheap & easy methods for generating hypothesis	• Cannot be used for hypothesis testing

□ Types of epidemiological study designs

1. Descriptive epidemiological study:

Descriptive epidemiology studies are relatively inexpensive to conduct and are usually of short duration. However, such studies are limited in their usefulness since no inferences can be made concerning causality.

Generally, descriptive epidemiology studies are sentinel devices are used to generate hypothesis or to provide evidence that indicates that whether there is sufficient cause for conducting a lengthier and costlier analytic study.

Eg: Case report, ecological studies

2. Analytic epidemiological study:

Although analytic epidemiological studies are more informative than the descriptive studies, they are expensive and time-consuming to conduct.

These type of studies commonly considered by CFSAN in safety evaluation include cross-sectional,

prospective and retrospective studies. Results from such studies, when available are in the overall safety evaluation of regulated products.

Eg: Cohort Study, Cross sectional studies, meta analysis

There are three main types of analytical epidemiological studies:

1. Prospective studies
2. Retrospective studies
3. Cross-sectional studies

→ refer to page 82 for more information:

#Drug Utilisation Review (DUR):

- DUR is a tool to identify problems in the medication use process i.e. drug prescribing, dispensing, administration and monitoring, according to the formulary and STG.

- As problems are identified, strategies are developed and implemented to improve the use of drugs.

- DUR also helps to monitor the rational use of drugs by knowing which drugs are properly used (according to the formulary) and for how long they are used (as described in STG).

The approach to develop a DUR programme, varies, but there are nine important steps to follow which are now well accepted.

Step 1: Establish responsibility for DUR process

The DTC committee usually takes the responsibility for DUR process.

- It can be allotted to a sub committee also if

DTC is preoccupied with other hospital responsibility

Step 2: Establish the scope of each study:

- Hospital pharmacists, nurses and physicians are major sources of suggestions for focusing DUR studies.

- For ex, DUR may study one medication such as ranitidine or a condition [use of antibiotics as prophylaxis medication for caesarean section].

- DUR might also focus on one step in medication use process such as prescribing, drug labeling or drug administration].

- The focus may shift from one area to another, from quarter to quarter or as and when one DUR study gets over.

- DUR usually focuses on drugs or therapies that are of high use, high cost, high risk to prone to a problem.

- May use A.B.C analysis to choose.

Step 3: Establish Criteria or Indicators for how the drug should be used or the condition treated:

- Criteria usually include the following components:
Use:

Appropriate indication, treatment of underlying conditions
~~Appropriate treatment of symptoms in treating under-~~
lying diseases.

Selection:

Efficacy, safety, total cost.

Dosing: Indication-specific dosing (age), indication-specific duration, dosing intervals.

Interaction: Disease, food, drug

Administration: Dosing interval, loading dose, maintenance dose, duration and withdrawal of medication.

Step 4: Collect and organise data:

- Data collection forms can be designed based on the criteria and made into a simple 'yes-or-no' or 'fill-in-the-blanks' questions format.

- Data collection for a DUR study within the hospital is often done by hospital pharmacist and his group or head nurse and her team.

- The most common data sources are patient charts, dispensing records, medication administration records and laboratory test records.

- It is important not to collect too much data, but to focus on specific indications related to the problem.

Step 5: Analyse the data:

- The data must be tabulated and reported in a standard format for comparison with ^{baseline} benchmarks. It is often necessary to create simple tables usually sorted by the most important indicator.

Step 6: Develop conclusions:

-The DTC committee would review the results and decide what needs to be done. DTC may also develop conclusions regarding reasons for differences between results and benchmarks.

Step 7: Make recommendations:

-The DTC committee reviews the results of the data analysis and develops conclusions regarding reasons for differences between results and benchmarks.

Step 8: Take Action:

-The DTC committee may recommend changes based on the audit to improve knowledge or change behaviour.

Step 9: Follow up:

-It is important to follow up actions decided

(★)

The pharmacist's role intervention DUE:

1. program development, ^{U;hw;fioha} supervision and co-ordination. (1, 2, 3)
2. education of hospital staff about DUE
3. promotion of the goals and objectives of DUE
4. Development of data collection instruments.
5. pilot test, data collection, analysis and report writing.
6. Documentation of program outcome
7. presentation of DUE results at meetings and conferences.
8. publication of results intervention peer-reviewed journals.

More info:

1. Descriptive epidemiology
2. Analytical epidemiology (observational)
3. Experimental epidemiology (interventional)

1. It helps to formulate the etiological hypothesis.
Ex: More than 2 drinks a day may rise the risk of endometrial carcinoma. This statement can be used to formulate the etiological hypothesis to establish the cause and effect relationship b/w consumption of alcohol for more than 2 times a day and endometrial

2. In observational studies, the researcher observes and systematically collects information but does not try to change the people (or animal or reagent) being observed.

3. But in experimental studies (interventional) the researcher intervenes to change something (Ex: gives some patients a drug) and then observes what happens

Case report:

Case: Case is defined as "a person in the population or study group identified as having the particular disease, health disorder or condition under investigation".

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

As used in pharmacoepidemiology, a case report describes a single patient who was exposed to a drug and experiences a particular usually adverse outcome.

Ex: one might see a published case report about a young woman who was taking oral contraceptives and who suffered a pulmonary embolism.

□ However, in a case report one cannot know if the patient reported is either typical of those with the exposure or typical of those with the disease. Certainly, one cannot usually determine whether the adverse outcome was due to the drug exposure or would have happened anyway.

• It is very rare that a case report can be used to

Case Report

make a statement about ^{دفعه} causation.

Exception-1:

One exception to this would be when the outcome is so rare and so characteristic of the exposure that one knows that it was likely to be due to the exposure, even if the history of exposure were unclear.

- An example of this is clear cell vaginal adenocarcinoma occurring in young women exposed in utero to diethylstilbestrol.

- Case reports can be particularly useful to document causation when the treatment causes a change in disease course which is reversible, such that the patient returns to his or her untreated state when the exposure is withdrawn, can be treated again, and when the change returns upon repeat treatment.

Exception-2:

Another exception would be when the disease course is very predictable and the treatment causes a clearly apparent change in this disease course.

• An example would be the ability of penicillin to cure streptococcal endocarditis, a disease that is nearly uniformly fatal in the absence of treatment.

• Consider a patient who is suffering from an overdose of methadone (a long-acting narcotic) and is comatose.

• If this patient is then treated with naloxone (a narcotic antagonist) and immediately awakens, this would be very suggestive that the drug indeed is efficacious as a narcotic antagonist.

• As the naloxone wears off the patient would become comatose again, and then if he or she were given another dose of naloxone the patient would awaken again.

• This, especially if repeated a few times, would represent strong evidence that the drug is indeed effective as a narcotic antagonist.

• This type of challenge-rechallenge situation is relatively uncommon.

• During their daily routine, practitioners notice the

emergence of an outcome and relate it to a drug exposure.

• The reporting of that event through an official reporting system or pharmacy journal generates a signal that alerts others to the possibility of causal association

Example:

- One of the most influential case reports was that by McBride (1961), which generated a signal later confirmed, that drugs could produce fetal abnormalities.
 - That report is responsible for the creation of teratology as a field of study.
 - New indications for drugs have also been identified through case reports.
 - For ex, Zappacosta (1980) reported a case report of a patient treated with minoxidil that was discovered to stimulate hair growth.
- Subsequently, a topical formulation of minoxidil was developed to take the advantage of that effect. It is now a successful product on the market.

Purpose of case reports:

- Impart important new knowledge

- Describe:

1. Unique or nearly unique cases
2. New diseases or syndromes
3. Unexpected associations
4. Unexpected events (good or bad) e.g. side effects of drugs
5. New diagnostic techniques or treatment options.

Advantages: cheap and easy method for generating hypothesis

Disadvantages: cannot be used for hypothesis testing.

Case Series:

Case series are collections of patients, all of whom have a single exposure whose clinical outcomes are then evaluated and described.

• Often they are from a single hospital or medical practice. Alternatively, case series can be collections of patients with a single outcome, looking at their antecedent exposures.

• For example, one might observe 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.

Purpose:

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

• 1st: they can be useful for ^{exposed, case series} quantifying the incidence of an adverse reaction.

• 2nd: they can be useful for being certain that any particular adverse effect of concern does, not occur.

Series
US

when observed in a population which is larger than that studied prior to drug marketing.

- The so-called "Phase IV" post marketing surveillance study of prazosin was conducted for the former reason, to quantify the incidence of first-dose syncope from prazosin.

- The "Phase IV" post marketing surveillance study of cimetidine was conducted for the latter reason.

- Metiamide was an H₂ blocker which was withdrawn after marketing outside the US because it caused agranulocytosis. Since cimetidine is chemically related to metiamide there was a concern that cimetidine might also cause agranulocytosis.

- In both examples, the manufacturer asked its sales representatives to recruit physicians to participate in the study.

- Each participating physician then enrolled the next series of patients for whom the drug was prescribed.

• In this type of study, one can be more certain that the patients are probably typical of those with the exposure or with the disease, depending on the focus of the study.

• However, in the absence of a control group, one cannot be certain which features in the description of the patients are unique to the exposure, or outcome.

• As an example, one might have a case series from a particular hospital of 100 individuals with a certain disease, and note that all were men over the age of 60.

• This might lead one to conclude that this disease seems to be associated with being a man over the age of 60.

• However, it would be clear that this would be an incorrect conclusion once one noted that the hospital this case series was drawn from was a Veterans Administration hospital, where most patients are men over the age of 60.

• In the previous example of pulmonary embolism and oral contraceptives, 30% of the women with pulmonary embolism had been using oral contraceptives.

• However, this information is not sufficient to determine whether this is higher, the same as, or even lower than would have been expected.

• For this reason, case series are also not very useful in determining causation, but provide clinical descriptions of a disease or of patients who receive an exposure.

Advantage: Easy quantization of incidence

Disadvantage: No control group, so cannot be used for hypothesis testing.

Cross Sectional Study:

- Cross sectional study may be of descriptive or analytical nature.
- Cross sectional study are also known as instantaneous studies, simultaneous studies or prevalence studies.

These are studies of use of drugs at the specific point of time and are conducted through surveys data base analysis or medication chart reviews.

They help the collection of data on a cross section of population, which may comprised the whole population or a population (sample) of it.

This type of studies provide information about the situation that exists at a single time.

An "observational" design that ^{observes} surveys exposures and disease status at a single point in time (a cross-section of the population).

• Often used to study conditions that are relatively frequent with long duration of expression (nonfatal, chronic conditions).

Cross
Sectional
Study

It measures prevalence, not incidence of disease.

Ex: Community surveys

• Not suitable for studying rare or highly fatal diseases or a disease with short duration of expression.

Advantage:

1. The studies can be short term
2. Relatively inexpensive to conduct
3. It can only measure disease prevalence rather than incidence.
4. They can provide a wealth of data that is of much used in health system research.

Disadvantage:

1. No direct estimate of risk and the scope for bias since exposure and disease are measured at the same point of time.
2. It is not possible to establish temporality, that is whether the exposure or presence of a characteristic preceded the development of the disease or condition.

Example

Statement of the problem: mental health problems are said to be common in the aftermath of a disaster and mental health problems are believed to be associated with physical damage.

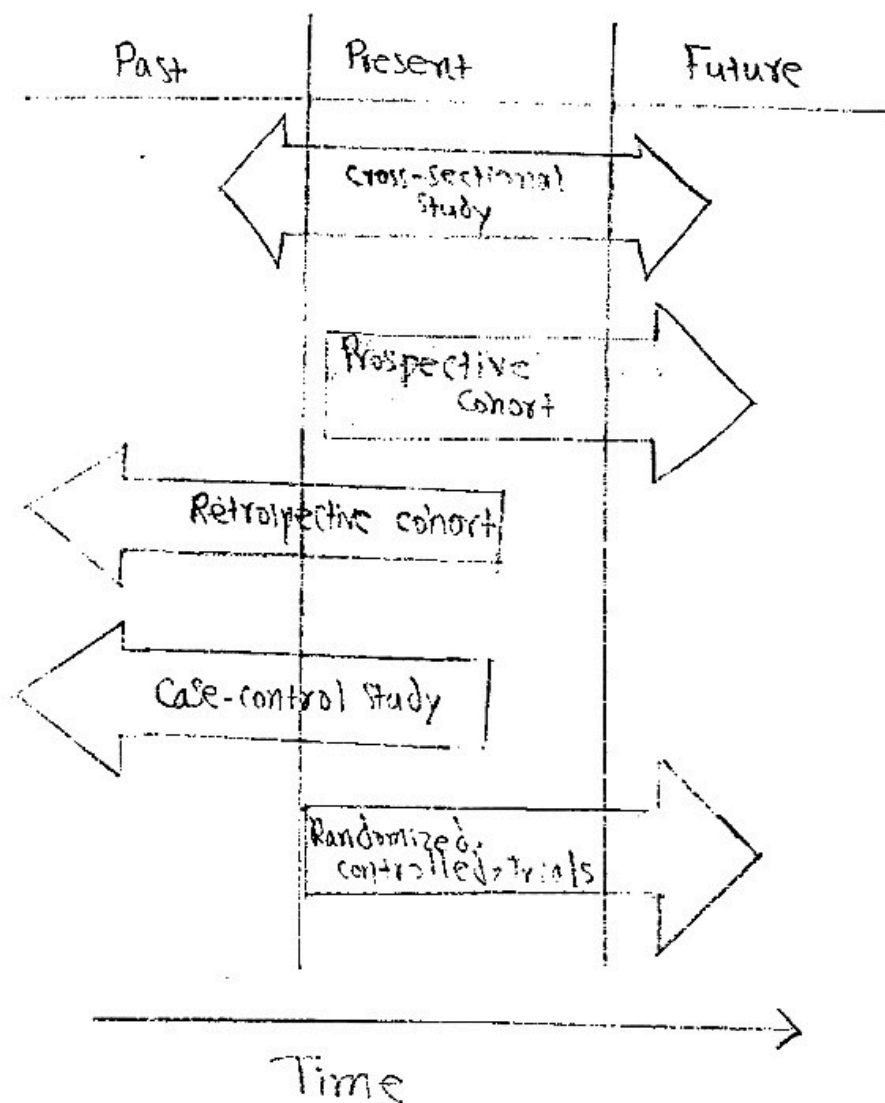
Aim: to describe the association between physical damage and mental health problems

Question: Are mental health problems associated with physical damage in time of disaster?

Hypothesis: Elderly people with poor mental health are more likely to have severe housing damage in time of disaster.

Example: A cross-sectional study can be used to look at the association between obesity and television watching. A sample of people from the population that you are interested in can be polled and asked about their height/weight ratio and the number of hours of television the person watches each week. This study will give insight as to
بینش

whether obesity and television watching are associated, but it will not help to determine which might cause the other. In other words, it is not known if obesity causes more television watching or if more television watching causes obesity.



the study groups follow a group of people who do not have the disease for a period of time and see who develops the disease (new incidence). The cohort cannot therefore be defined at a group →

Cohort Study:

Cohort Study are studies that identify ^{exposed} subsets of a define population and follow them over time, looking for differences in their outcome.

Cohort studies generally are used to compare exposed patients to unexposed patients, although they can also be used to compare one exposure to another.

• The term cohort is defined as the group of people who share a common characteristic or experience within the defined time period e.g. Age, occupation, exposure to a drug or vaccine, pregnancy, insured person.

• For example, one could compare women of reproductive age who use oral contraceptives to users of other contraceptive methods, looking for the differences in the frequency of venous thromboembolism. When such studies were performed, they in fact confirmed the relationship between oral contraceptives and thromboembolism, which had been noted using analyses of secular trends and case-control studies.

Example

- A cohort study was designed to assess the impact of sun exposure on skin damage in beach volleyball players.
- During a weekend tournament, players from one team wore waterproof, SPF 35 sunscreen, while players from the other team did not wear any sunscreen. At the end of the volleyball tournament players' skin from both teams was analyzed for texture, sun damage, and burns.
- Comparisons of skin damage were then made based on the use of sunscreen. The analysis showed a significant difference between the cohorts in terms of the skin damage.

Indication for Cohort Studies:

- A. When there is good evidence of an association between an exposure and disease, as derived from clinical observations and supported by descriptive and case control studies.

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

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

D. When ample funds are available.

Framework of a cohort study:

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

Cohort	Yes (disease)	No (disease)	Total
Exposed to putative etiologic factor	a	b	$a+b$
Not exposed to putative etiologic factor	c	d	$c+d$

Type of cohort study:

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

1. Prospective cohort study:

A prospective cohort study or current cohort study is one in which the outcome (eg Disease) has not yet occurred at the time the investigation begins.

• Most prospective studies begin in the present and continue into future.

• For eg. The long term effects of exposure to uranium was evaluated by identifying a group of uranium miners and a comparison group of individual not exposed to uranium mine and by assessing subsequent development of lung cancer in both the groups.

2. Retrospective cohort study:

A retrospective cohort study or historical cohort

Study is one in which the outcomes have all occurred before the start of the investigation.

- The investigator goes back in time, sometimes 10 to 30 years, to select his study groups from existing records of past employment, medical or other records and traces them forward through time, from a past date fixed on the records, usually up to the present.

3. Combination of retrospective and prospective cohort study:

In this type of study, the retrospective and prospective elements are combined.

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

Cohort study example:

- The news's health study followed more than 160,000 American nurses over time, starting in

1976. The exposure of interest was oral contraceptive use.

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

Advantages of cohort Studies:

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

Disadvantages:

1. Studies involve a large no. of people
2. It takes a long time to complete the study
3. certain administrative problems such as loss of experienced staff, loss of finding.
4. There may be changes in the standard methods

or diagnostic criteria of the disease over prolonged follow-up.

5. The study itself may alter people's behavior

6. Expensive

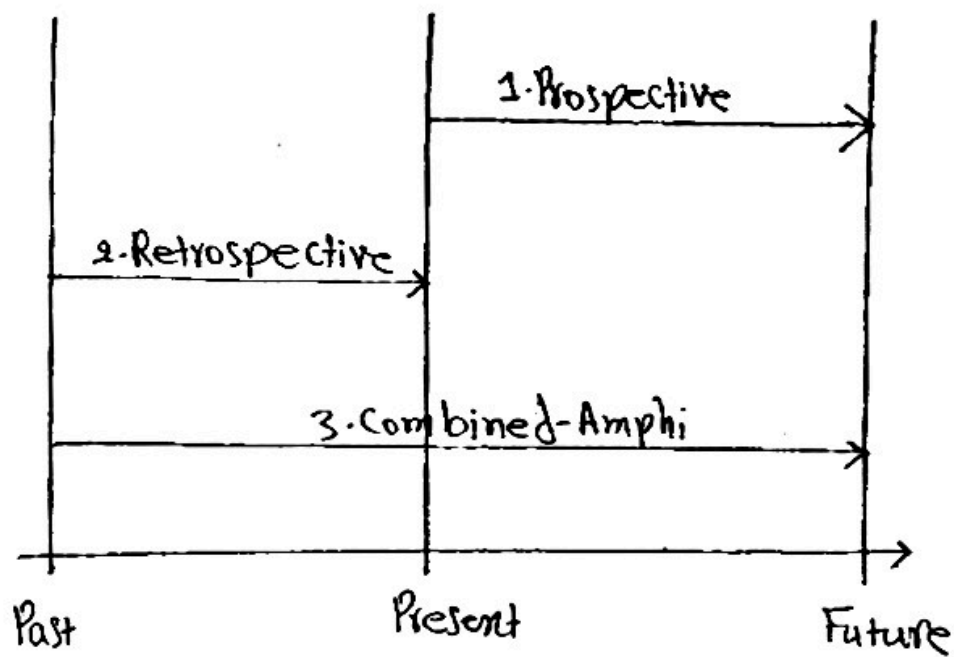


Fig: Types of cohort study

Non experimental Studies (observational):

1. Descriptive non experimental Studies

A. Case reports B. Case Series

2. Analytical non-experimental Studies

A. Case control B. Cohort Study C. Cross-sectional Study

Case control:

- By definition, a case control study involves two population - case and control
- In this study, cases and controls must be comparable with respect to known "confounding factor" such as age, sex, occupation, social status
- Case-control studies are studies that compare cases with a disease to controls without the disease, looking for differences in antecedent exposure.

Example

One could select cases of young women with venous thromboembolism and compare them to controls without venous thromboembolism, looking

for differences in antecedent oral contraceptive use. Several such studies have been performed, generally demonstrating a strong association between the use of oral contraceptive and venous thromboembolism.

Ex

There is a suspicion that zinc oxide, the white non-absorbent sunscreen traditionally worn by lifeguards is more effective at preventing sunburns that lead to skin cancer than absorbent sunscreen lotions.

A case-control study was conducted to investigate if exposure to zinc oxide is a more effective skin cancer prevention measure. The study involved comparing a group of former lifeguards that had developed cancer on their cheeks and noses (cases) to a group of lifeguards without this type of cancer (controls) and assess their prior exposure to zinc oxide or absorbent sunscreen lotions.

This study would be retrospective in that the former

lifeguards would be asked to recall which type of sunscreen they used on their face and approximately how often.

- In case control, matching is important.
- Case control studies are used when outcomes and exposure to the drug are rare.

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

• Some example of case control studies that could establish the association b/w the drugs and adverse events are:

- Diethylstilbestrol (DES) and vaginal cancer
- Aspirin and Reye's Syndrome
- NSAIDs and peptic ulcer
- Oral contraceptives and venous thromboembolism

→ Data from case control studies are used to calculate an odds ratio, which is the ratio of the odds of developing the disease for exposed patient to the odds of developing the disease for unexposed patients.

The basic design of a case control study is

Suspected or risk factors	Cases (disease present)	Control (disease absent)
Present	a	b
Absent	c	d
	a+c	b+d

It is a 2×2 table which provides a very useful framework to discuss the various elements which make up a case control study.

• To illustrate, if it is our intention to test the hypothesis that cigarette smoking causes lung cancer, using the case control method, the investigation begins by assembling a group of lung cancer cases (a+c) and a group of suitably matched control (b+d).

• One then explores the past history of these two groups for the presence or absence of smoking, which is suspected to be related to the occurrence of the lung cancer.

• If frequency of smoking, $a/(a+c)$ higher in cases

than in controls, $b/(b+d)$, an association is said to exist between smoking and lung cancer.

Advantage and disadvantages:

Advantages:

1. relatively easy to carry out
2. Rapid and inexpensive
3. Require comparatively few subjects
4. Particularly suitable to investigate rare disease.
5. No risk to Subjects
6. Allows the study of several different etiological factors (e.g. smoking, physical activity and personality characteristics in myocardial infarction).
7. Risk factors can be identified rational prevention and control programs can be established.
8. No attrition problems, because case control studies do not require follow up of individuals in to the future.
9. Ethical problems minimal.

Disadvantages:

1. Problems of bias relies on memory or past records, the accuracy of which may be uncertain, validation of information obtained is difficult or sometimes impossible.
2. Selection of an appropriate control group may be difficult.
3. We cannot measure incidence and can only estimate the relative risk.
4. Do not distinguish b/w causes and associated factors.
5. Not suited to the evaluation of therapy or prophylaxis of disease.
6. Another major concern is the representativeness of case and controls.

The odds ratio is the ratio of ^{odds} odds of an event occurring in one group to the odds of it occurring in another group.

MAIN DIFFERENCE BETWEEN CASE CONTROL AND COHORT STUDIES

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

Meta-analysis is a statistical technique for combining the findings from 111 independent studies.

Meta Analysis

- Meta-analysis has been defined as "the statistical analysis of a collection of analytic results for the purpose of integrating the findings".
- It is used to identify sources of variation among study findings and, when appropriate, to provide an overall measure of effect as a summary of those findings.
- Meta-analysis may be regarded as a "STATE-OF-THE-ART" with Literature Review employing Statistical methods in conjunction with a thorough and Systematic qualitative Review.
- Meta-analysis provides the conceptual and quantitative framework for rigorous literature reviews.
- The most popular conception of meta-analysis is the summary of a group of randomized clinical trials dealing with a particular therapy for a particular disease.
- Typically, a meta-analysis would present an overall measure of the efficacy of treatment e.g. a summary odds ratio.

Purpose of Meta-analysis:

- To overcome publication bias and objectively present all relevant trials.
- To resolve apparent conflicts in results of several trials.
- To overcome inadequate size of individual trials
- To examine endpoints requiring larger samples than individual trials gathered
- To evaluate generalizability of conclusion
- To determine if new trials are needed.

General Steps involved in conducting a meta analysis:

1. Define the purpose
2. Perform the literature search
3. Establish inclusion/exclusion criteria
4. collect the data
5. Perform Statistical analyses
6. Formulate conclusions and recommendations.

1. Define the purpose:

It is particularly important to define precisely and in advance of its:

- Conduct the primary and secondary objectives of a meta analysis.

2. Perform the literature search:

While computerized searches of the literature can facilitate the retrieval of all relevant published studies these searches are not always reliable.

Use of search terms that are too nonspecific can result in large numbers of mostly irrelevant citations that need to be reviewed to determine relevance, whereas use of too many restrictions can result in missing a substantial number of relevant publications.

The help of a trained professional librarian, a review of the relevant reference sections of retrieved publications, and hand searches of relevant journals are recommended.

3. Establish inclusion/Exclusion criteria:

• A set of rules for including and excluding studies from the meta-analysis should be defined during the planning stage of the meta-analysis and should^{be} based on the specific hypotheses being tested in the analysis.

• A key point is that exclusion criteria should be based on prior considerations of design of the original studies and completeness of the reports and specifically not on the results of the studies.

• Another important note is that studies may often generate more than one published paper. It is essential that only one report on the same patients be accepted into the meta-analysis.

• The inclusion of a study more than once would assign undue weight to that study in the summary measure.

4. Collect the Data:

• When the relevant studies have been identified

and retrieved, the important information regarding study design and outcome needs to be extracted and recorded on data abstraction forms.

- Careful specification in the protocol for the meta-analysis of the design features and patient characteristics that will be of interest may help to avoid over or under collecting information.

- Many articles on "how to do a meta-analysis" recommend that the meta analyst assess the quality of the studies being considered in a meta-analysis using formal quality scoring systems.

5. Perform Statistical Analyses:

- In most situations, the statistical methods for the actual combination of results across studies are fairly straightforward.

- A basic principle in most analytic approaches is that the comparisons b/w treated (exposed) and untreated (unexposed).

- In any meta-analysis, the possible existence of

heterogeneity among study designs and results should be examined, and may warrant a set of exploratory analyses designed to investigate the sources of that heterogeneity.

Methods:

One might ^{investigate} stratify the studies according to patient characteristics or study design features and investigate heterogeneity within and across data.

In addition to stratification, regression methods such as weighted least-squares linear regression could be used to explore sources of heterogeneity.

6. Formulate conclusion and recommendation:

Conclusions of a meta-analysis should be clearly summarized, with appropriate interpretation of the strengths and weaknesses of the meta-analysis:

Authors should clearly describe the:

- Population(s) to which the results apply
- How definitive the results are

- should outline the areas that need future research
- Investigation of adverse effects
- New indications for existing therapy
- Differential effects among subgroup patients
- Selection from among several alternative therapies
- Saving time and money

Advantages:

1. Derivation and statistical testing of overall factors
2. Generalization to the population of studies
3. Ability to control for b/w-study variation
4. Including moderators to explain variation

Applications of meta-analysis:

1. Investigation of Adverse effects:

Meta-analysis provides the benefit of vastly increased statistical power to investigate adverse events.

The assessment of the excess risk of gastrointestinal side effects associated with NSAIDs provides an

excellent example of a situation in which meta-analysis has been helpful.

2. New indications for existing therapies:

Meta-analysis has also been used to assess the effectiveness of existing therapies for new indications.

As an example:

• The efficacy of anti-lymphocyte antibodies in the preoperative period of cadaveric kidney transplantation (induction therapy)

• Individual studies, both randomized and non-experimental had failed individually to show a significant benefit of induction therapy with respect to allograft survival.

• Szczech and colleagues (1977) performed a meta-analysis of the published data from the randomized trials of induction therapy in adults receiving cadaveric renal transplants.

3. Selection from among several alternative therapies:

• In a meta-analysis of therapies for the prevention of supraventricular arrhythmias after coronary bypass surgery, Andrews et al. (1991) looked separately at verapamil, digoxin and adrenoceptor blockers as prophylactic agents.

Only randomized trials were included. Neither digoxin nor verapamil reduced the risk of supraventricular arrhythmias after coronary artery bypass surgery.

• The risk of a supraventricular arrhythmia in patients treated with beta-blockers was dramatically reduced although significant heterogeneity among the study results was present.

4. Saving time and Money:

One of the potential benefits of meta-analysis is the possibility of shortening the time b/w a medical research finding and the clinical implementation of a new therapy.

This is a concern not only for the development of new drugs, but for the exploration of new

indications for existing therapies.

Case example:

The application of meta-analysis in Assessing Adverse events:

Background

• It would be desirable to choose a drug and dose with a comparatively low risk of gastrointestinal effects to reduce NSAID toxicity in populations.

Questions

- Can one compare relative risks of serious gastrointestinal complications across individual NSAIDs?
- To what extent differences in toxicity be related to different doses (or "dose equivalents")?

Approach

- Perform meta-analysis to examine relative risks for particular NSAIDs.
- Weighted ranking System that incorporates study size into the weights implemented.
- Comparisons among NSAIDs were indirect, as

very few head-to-head studies were available.

Results:

- Relative risks for all NSAIDs were significantly greater than 1.0.
- Weighted analysis showed ibuprofen with the lowest and ketoprofen with the highest risks.
- High dose ibuprofen also was associated with elevated relative risk.

Strengths:

- Systematic review of all relevant data.
- Can apply weights to studies.

Limitations:

Indirect comparisons to ibuprofen depend on assumptions about similarities of populations studied. Indifferent studies.

- Analysis limited to studies available (only studies that compared to ibuprofen as reference were selected).

• Summary Points:

By using meta-analysis, one can systematically review NSAID side effects for specific drugs.

- Studies can be weighted according to their size.
- Systematic review may provide us with helpful information in clinical decision making.

Strengths of meta-analysis

- Can summarize from available studies the effects of interventions across many patients.
- Can determine if the effect of the intervention is sufficiently large in practical as well as statistical terms.
- Can reduce uncertainty of interpretation
- Can allow more objective assessment of evidence and thereby reduce disagreement
- Can reduce false negative results and thereby hasten introduction of effective treatments into clinical practice.
- Can clarify heterogeneity between study results.

- Can suggest promising research questions for future study
- Can assist accurate calculation of sample size needed in future studies.
- Can increase precision of literature reviews

Weaknesses

- Can pass along inflated estimates of size effects based on (a) research design characteristics, (b) published v.s. unpublished study composition and (c) small sample sizes.
- Can be limited by unspecified "black box" treatment and control conditions as well as lack of attention to potential interactions with subject characteristics, range of outcomes, and temporal factors
- Can be compromised by inclusion of non-peer-reviewed data - especially if derived from biased sources, e.g. the pharmaceutical industry.
- Application of the results of meta-analysis to individual patients remains a difficult judgment

call because "uncertainty with respect to a particular patient will always be greater than with respect to the overall patient group."

- Cannot overcome subjectivity in choice of outcomes and their weighting in analysis.

- The combined statistically significant estimate of size effect may still prove inconclusive because of ignorance or uncertainty about other relevant matters.

Random error is an error in measurement caused by factors which vary from one measurement to another. These changes may occur in the measuring instruments or in the environmental conditions. Ex of cause: electronic noise in the circuit of an electrical instrument

Random Error:

- Random error is the result of fluctuations around a true value because of sampling variability.
- It can occur during data collection, coding, transfer or analysis.
- Examples of random error include: poorly worded questions, a misunderstanding in interpreting an individual answer from a particular respondent, or a typographical error during coding.
- Random error affects measurement in a transient, inconsistent manner and it is impossible to correct for random error.
- There are two basic ways to reduce random error in an pharmacoepidemiological study:
 - The first is to increase the sample size of the study. In other words, add more subjects to your study.
 - The second is to reduce the variability in measurement in the study. This might be accomplished by

⊛ A false or mistaken result obtained in a study or experiment = Error

If we are to compare method A with method B about its superiority and if we proceed on the assumption that both methods are equally good, then this assumption is termed as the null hypothesis. As against this, we may think that the method A is superior or the →

using a more precise measuring device or by increasing the number of measurements.

EXAMPLE

Measuring height:

→ Measuring tape held differently by different investigators

→ loss of precision

○ error

→ Tape shrunk/wrong

→ systematic error

○ bias (cannot be corrected afterwards)

Statistical error: Type I and Type II

• Statisticians speak of two significant sorts of Statistical error.

• The context is that there is a "null hypothesis" which corresponds to a presumed default "state of nature" e.g., that an individual is free of disease, that an accused is innocent.

• Corresponding to the null hypothesis is an alternative hypothesis which corresponds to the

→ method B is inferior, we are then stating what is termed as alternative hypothesis.

opposite situation, that is that the individual has the disease, that the accused is guilty.

- The goal is to determine accurately if the null hypothesis can be discarded in favor of the alternative.

- A test of some sort is conducted (a blood test, a legal trial) and data are obtained. The result of the test may be negative (that is, it does not indicate disease).

- On the other hand, it may be positive (that is, it may indicate disease, guilt). If the result of the test does not correspond with the actual state of nature, then an error has occurred, but if the result of the test corresponds with the actual state of nature, then a correct decision has been made.

- There are two kinds of error, classified as "type I error" and "type II error", depending upon which hypothesis has incorrectly been identified as the true state of nature.

Type I error

Type I error, also known as an "error of the first kind" or a α error, or a "false positive": the error of rejecting a null hypothesis when it is actually true. In other words, Type I error can easily be said as "A Positive Assumption is False".

Type II error

Type II error, also known as an "error of the second kind" or a β error, or a "false negative": the error of failing to reject a null hypothesis when it is in fact not true. In other words, this is the error of failing to observe a difference when in truth there is one, thus indicating a test of poor sensitivity. An example of this would be if a test shows that a woman is not pregnant, when in reality, she is. Type II error can be viewed as the error of excessive skepticism.

In other words, Type II error can also be easily be said as "A Negative assumption is False".

Measurement error:

• Errors in measuring exposure or disease can be an important source of bias in epidemiological studies. In conducting studies, therefore, it is important to assess the quality of measurements. An ideal survey technique is valid (that is, it measures accurately what it purports to measure). Sometimes a reliable standard is available against which the validity of a survey method can be assessed.

For example, a sphygmomanometer's validity can be measured by comparing its readings with intra arterial pressures and the validity of a mammographic diagnosis of breast cancer can be tested (if the woman agrees) by biopsy.

Analysing validity

When a survey technique or test is used to dichotomise subjects (for example, as cases or non-cases, exposed or not exposed) its validity is analysed by classifying subjects as positive or negative, firstly by the survey method and secondly according to the standard reference test. The findings can then be expressed in a contingency table as shown below.

Table : Comparison of a survey test with a reference test			
Survey test result	Reference test result		Totals
	Positive	Negative	
Positive	True positives, correctly identified = (a)	False positives = (b)	Total test positives = (a + b)
Negative	False negatives = (c)	True negatives correctly identified = (d)	Total test negatives = (c + d)
Totals	Total true positives = (a + c)	Total true negatives = (b + d)	Grand total = (a + b + c + d)

From this table four important statistics can be derived:

Sensitivity A sensitive test detects a high proportion of the true cases, and this quality is measured here by $a/a + c$.

◦ Specificity - A specific test has few false positives, and this quality is measured by $d/b+d$.

Systematic error - For epidemiological rates it is particularly important for the test to give the right total count of cases. This is measured by the ratio of the total numbers positive to the survey and the reference tests, or $(a+b)/(a+c)$.

◦ Predictive value - This is the proportion of positive test results that are truly positive.

◦ It should be noted that both systematic error and predictive value depend on the relative frequency of true positives and true negatives in the study sample (that is, on the prevalence of the disease or exposure that is being measured).

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

Bias

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 which would have been obtained from including the entire study base.

Selection bias is a problem in clinical studies, which

◦ In Survey Sampling, the bias that results from an unrepresentative sample is called selection bias.

are not randomised.

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

- علاج - علاج
- 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, e.g. 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.

Eg: A patient taking nonsteroidal anti-inflammatory drugs and presenting with abdominal pain, may

be more likely to be suspected as having a gastric ulcer. This patient is therefore more likely to be sent to the hospital for tests for this diagnosis than other patients with similar pain who are not using nonsteroidal anti-inflammatory drugs. A study using patients in the hospital may thus show a strong, but biased, association between mild nonbleeding gastric ulcers and the use of nonsteroidal anti-inflammatory drugs.

2. 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.

D- Protopathic bias is a term that was first used by Feinstein (1985). It may occur if a particular treatment or exposure was started, stopped or otherwise changed because of the baseline manifestation caused by a disease or other outcome event.

Eg: For instance, people could stop taking aspirin because of the presence of blood in their stools. If the presence of blood were the first expression of colon cancer, we would subsequently find a negative association between current aspirin use and colon cancer.

2. Information Bias:

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

confounding: caused

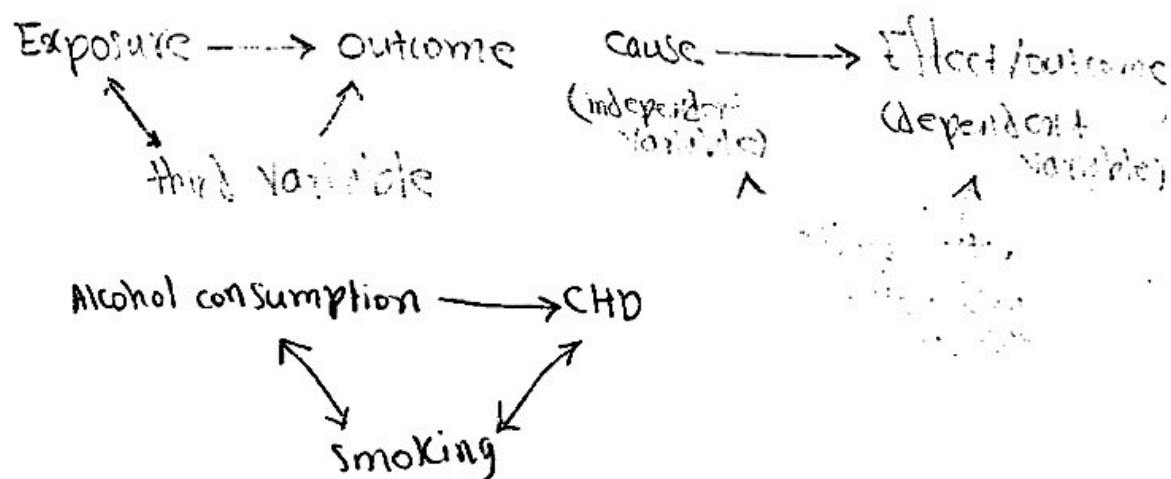
3. Confounding Bias:

Confounding occurs when the estimate of a measure of association between drug exposure and health 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 factor 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. A confounding variable is a variable other than the risk factor, which is related independently to both the risk factor, and the outcome variable.

In the case of cigarette smoking and lung cancer, one can find a very strong association of having yellow fingertips and development of lung cancer. It is an indirect association confounded by cigarette smoking. Cigarette smoking causes both yellow fingertips and lung cancer.

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



Spontaneous Reporting:

All ^{not asked for and often not wanted} unsolicited reports from health care professionals or consumers, received by the FDA via either the voluntary or mandatory route are called spontaneous reports.
Something that is mandatory must be done.

In order to ensure that safe and effective pharmaceuticals are available, the FDA ^{to trust or depend on someone or something} relies on both the recognition and voluntary reporting of serious adverse events (AEs) by health care providers and their patients and the mandatory Reporting of AEs by manufacturers as required by law and regulation.

The individual spontaneous reports of:

- i- adverse drug reactions (ADRs)
- ii- Medication errors
- iii- product quality problems, sent directly to the FDA through the Med Watch program or to the manufacturer and then indirectly from the manufacturer to the FDA, combined with data from formal clinical studies and from the medical and scientific

Spontaneous Reporting

literature, comprise the primary data source upon which postmarketing surveillance depends.

The FDA has determined that the product's benefits ^{to be more important or valuable than the else (verb)} outweigh any known or anticipated risks for the general population when the product is used as indicated in the approved prescribing information.

All these cases - individual case safety reports (ICSRs) are entered on the company's safety database and on regulatory authority's safety database.

They are examined individually and the aggregate for a product in order to identify clusters of reports that could represent signal of previously unknown adverse reaction or drug interaction or some changes in character of a known adverse effect. It may also be possible to recognize a new risk factor for a reaction to a product, such as subgroup of patients at particular risk.

Of all the sources of data for a drug safety monitoring, the Spontaneous Reporting System, provides the highest volume of information at

the lowest maintenance cost.

The strengths and weakness of spontaneous reporting system is as below:

Strengths:

1. low set up & running Cost.
2. allows for ^{continuous} perpetual Monitoring of all drugs After marketing.
3. may generate rapid ^{alerts} Alerts and stimulate Follow-up.
4. doesn't limit monitoring To specific patient grp..
5. least likely to influence Prescribing behaviour.

Weaknesses:

1. under reporting is major Problem.
2. no direct information.
3. sensitive to selective reporting.
4. quality of info can vary & can prevent proper evaluation.
5. depend on reporters to identify an event as a reaction to a drug.

- the Yellow Card Scheme is the UK system for collecting information on suspected adverse drug reactions (ADRs) to medicines.

• The system for spontaneous reporting is the yellow card ^{system} Schemes (YCS). the principles of this reporting scheme were such that:

1. Suspected adverse reactions should be reported with no establishment of causality.
2. It is a responsibility of all doctors and dentists to report suspected adverse reactions.
3. All reports should be prompt.
4. All reports are treated in confidence.

Application:

Major function of spontaneous reporting system is generation of "new signals".

- A signal is defined by WHO as "reported information on possible causal relationship b/w an adverse event and a drug".

The relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal depending upon the seriousness of the event and

In Confidence

YellowCard

COMMISSION ON HUMAN MEDICINES (CHM)

It's easy to report online at
www.mhra.gov.uk/yellowcard



REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in the British National Formulary (BNF) or www.mhra.gov.uk/yellowcard for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials: _____ Sex: M / F Is the patient pregnant? Y / N Ethnicity: _____
Age (at time of reaction): _____ Weight (kg): _____ Identification number (e.g. Practice or Hospital Ref): _____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome
Recovered ☐
Recovering ☐
Continuing ☐
Other ☐

Date reaction(s) started: _____ Date reaction(s) stopped: _____
Do you consider the reaction(s) to be serious? Yes / No
If yes, please indicate why the reaction is considered to be serious (please tick all that apply):
☐ Patient died due to reaction ☐ Involved or prolonged inpatient hospitalisation
☐ Life threatening ☐ Involved persistent or significant disability or incapacity
☐ Congenital abnormality ☐ Medically significant, please give details: _____
If the reactions were not serious according to the categories above, how bad was the suspected reaction?
☐ Mild ☐ Unpleasant but did not affect everyday activities ☐ Bad enough to affect everyday activities

OTHER DRUG(S) (including self-medication and complementary remedies)

Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No
If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS

Name and Professional Address: _____

Postcode: _____ Tel No: _____
Email: _____
Speciality: _____
Signature: _____ Date: _____

CLINICIAN (if not the reporter)

Name and Professional Address: _____

Postcode: _____ Tel No: _____
Email: _____
Speciality: _____
Date: _____

Information on adverse drug reactions received by the MHRA can be downloaded at www.mhra.gov.uk/daps
Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at www.mhra.gov.uk/drugsafetyupdate

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

FREEPOST YELLOW CARD

SECOND FOLD HERE

GUIDELINES FOR YELLOW CARD REPORTING

Please use the Yellow Card Scheme to tell us about:

- All suspected adverse drug reactions for new medicines - identified by the black triangle ▼ symbol
- All suspected adverse drug reactions occurring in children, even if a medicine has been used off-label
- All serious* suspected adverse drug reactions for established vaccines and medicines, including unlicensed medicines, herbal remedies, and medicines used off-label
- All medication errors that result in an adverse reaction

*Reactions which are fatal, life-threatening, a congenital abnormality, disabling or incapacitating, result in or prolong hospitalisation, or medically significant are considered serious.

If you are unsure, please report anyway

For more information:

- Contact the Yellow Card Information Service on Freephone 0800 731 6789
- Visit the Yellow Card website – www.mhra.gov.uk/yellowcard

FIRST FOLD HERE

1 About the suspected side effect

What were the symptoms of the suspected side effect, and how did it happen? If there isn't enough space here, attach an extra sheet of paper.

How bad was the suspected side effect? Tick the box that best describes how bad the symptoms were.

- ☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities ☐ Bad enough to see doctor
☐ Bad enough to be admitted to hospital ☐ Caused very serious illness ☐ Caused death ☐ Other

When did the side effect start?

How is the person feeling now? Tick the box that best describes whether the person still has symptoms of the suspected side effect.

- ☐ Better (no more symptoms) ☐ Getting better ☐ Still has symptoms ☐ More seriously ill ☐ Died ☐ Other

Can you give any more details? For example, did the person take or receive any other treatment for the symptoms? Did they stop taking the medicine as a result of the side effect?

2 About the person who had the suspected side effect

Who had the suspected side effect?

- ☐ You ☐ Your child ☐ Someone else

Information about the person Supply as much information as you can, even if you prefer not to give a name.

First name or initials _____ Family name _____ ☐ Male ☐ Female

Age _____ Weight _____ ☐ kg ☐ stones/pounds Height _____ ☐ metres ☐ feet/inches

Any other relevant information? For example, does the person have any medical conditions or allergies?

3 About the medicine(s) which might have caused the side effect

Give details of the medicine you suspect of causing the side effect.

Name of the medicine _____

☐ prescription

☐ bought in pharmacy

☐ bought elsewhere

Dosage (for example, one 250 mg tablet, twice a day) _____

bought on the internet

What was it taken for? _____

Start date: _____

End date: _____

Did you stop because of side effects? ☐ Yes ☐ No

If you (or the person you're reporting for) were taking any other medicine at the same time (which might have caused an interaction), give details of it. If you need to give details of more than one other medicine, attach an extra sheet of paper.

Name of other medicine _____

☐ prescription

☐ bought in pharmacy

☐ bought elsewhere

Dosage (for example, one 250 mg tablet, twice a day) _____

bought on the internet

What was it taken for? _____

Do you think this medicine might also have caused the side effect? ☐ Yes ☐ No ☐ Possibly

Start date: _____

End date: _____

Did you stop because of side effects? ☐ Yes ☐ No

Have you taken any other medicines or herbal remedies (as well as the above) within the last 3 months? ☐ Yes ☐ No

4 About your doctor (optional)

Would you like a copy of this report to be sent to your doctor?

☐ Yes

☐ No

If Yes, give the doctor's name and address.

Doctor's name _____

If you want us to send a copy of this report to any other healthcare professional, attach a separate sheet with their contact details.

Address _____

If we need more medical information (such as test results), do we have your permission to contact your doctor directly for it?

☐ Yes

☐ No

Postcode _____

5 About you – the person making the report

We need contact details – please supply a full postal address, even if you prefer not to give a phone number or email address.

Title _____

First name or initials _____

Family name _____

Address _____

Postcode _____

Telephone number _____

Email address _____

Please sign and date this form

I agree that the Medicines and Healthcare products Regulatory Agency (MHRA) can contact me to discuss the suspected side effect, and to ask for more information that might help understanding of the case.

Signed _____

Date _____

Prescription Event Monitoring (PEM):

Borne out of the need to monitor drug safety post marketing the PEM scheme was proposed separate from the yellow card scheme to provide the information on a population of defined size, enabling the incidence of events to be established with some degree of accuracy. A fundamental limitation of the yellow card scheme (spontaneous reporting) is the onus placed on the reporter to suspect that an adverse event is caused by a drug, the PEM circumvents this by requesting that all the events are reported and not just the suspected adverse effects.

PEM is a non-interventional, observational cohort form of pharmacovigilance. It is non-interventional in the sense that nothing happens to interfere with the doctor's decision regarding which drug to prescribe for each individual patient.

An event is defined as a particular untoward ^{adverse} happening experienced by a patient, undesirable

Event: an adverse or damaging medical occurrence.

either generally or in the context of his disease. The main objective of the PEM scheme is to recruit the first 10,000 recipients of a new drug and monitor them for the occurrence of any events.

The PEM process:

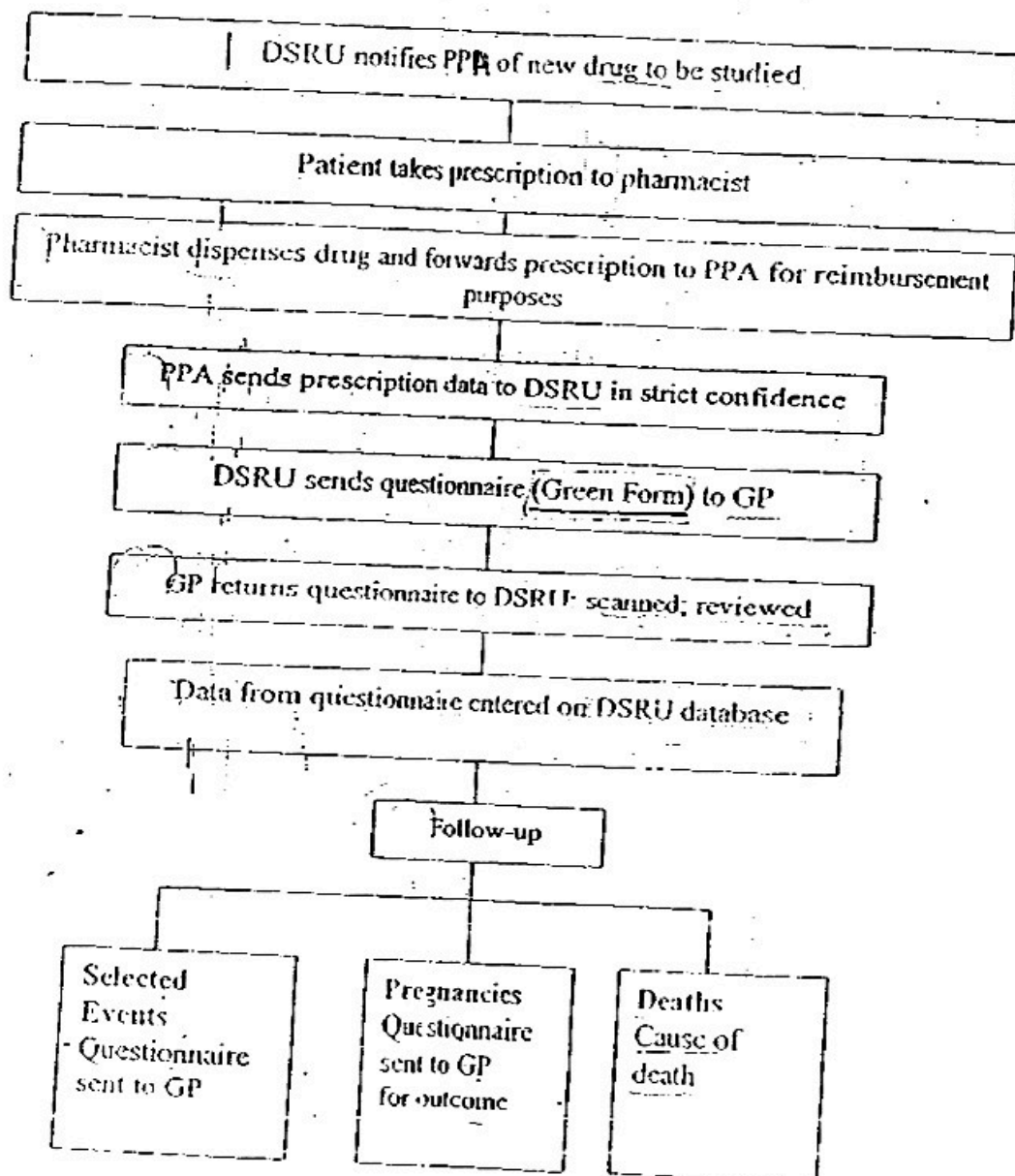
Prescription written by a General Practitioner (GP) are taken by the patient to a pharmacy to be dispensed. All prescriptions are routinely sent to the Prescription Pricing Authority (PPA) by the Pharmacist. The PPA then sends electronic copies of the prescription of the drug under study to the Drug Safety Research Unit (DSRU). By this process the information on patients exposed to the drug in question is obtained (exposure data), and this collection process continues until a cohort of 20,000 to 30,000 patient data is captured. The prescriber is sent a "Green Form" 3 to 12 months after the prescription was written. This form requests the details of any events that may have occurred to the patient.

Since the prescription was written. The forms are anonymised to preserve patient confidentiality. The events information on the forms provides the outcome data. The details of events and their incidences are then analyzed, and may result in the generation of signals, hypotheses or the initiation of follow-up studies. PEM is essentially a powerful hypothesis-generating method of pharmacovigilance, with which both exposure and outcome data of the real-life use of the drug in a large patient are obtained.

Advantages:

- PEM is inherently non-interventional
- An effective cohort is created on a national scale
- There are no exclusion criteria, so the clinical experience reflects the real life clinical experience of the drug in the general population.
- Reports are not required to make a decision as to a possible association of an event with a drug.

The process of collecting the events is illustrated in the diagram below



• Very long or even life-time follow-up can be undertaken to determine long-latency adverse reaction.

Disadvantages:

- The return rate of the Green Forms is below 60% with just more than half of these (52%) containing clinically-relevant data.
- Hospitals are not included in the scheme, therefore PEM is blind to therapies initiated and stopped in hospital care.
- There is no assurance of patient compliance to treatment with specific drug.
- Careful consideration of data and trends is essential to remove effect of any confounders.

~~Applications~~

1. incidence density:

PEM provides a numerator (the number of reports) and a denominator (the number of patient weeks or

months of exposure), both collected within known time frame (the difference, for each patient, b/w the start and stop dates of drug being monitored).

The incidence density (ID) for a given time period, is as follows:

$$ID_t = \frac{\text{Number of events during treatment for period } t}{\text{Number of patient months of treatment for period } t} \times 1000$$

The ID_s are then ranked to give estimates of the frequency of reported events.

2. Comparison of reasons for withdrawal and incidence densities:

The green form asks the doctors to specify the reasons for stopping the drug being monitored if, in fact, treatment was stopped.

3. The outcome of exposed pregnancies:

All pregnancies reported during PEM studies are followed up by the medical and scientific staff of OSRU in order to determine the outcomes in those

* Signal: A measurable or recognisable indicator of an event or process.

babies exposed in utero to the drugs being monitored. These data will soon be published in final and amended form because they add substantially to those currently available.

This work is of interest as these observational data may be of special value to those who need to advise on the care and continuation of pregnancies exposed to newly marketed medicines.

4. Generation and ^{evaluation} exploration of signals:

Signals can be generated by an event having an unusually high ID ranking in the reasons for stopping medication. Alternatively, it may be noticed that the pattern of the number of reports from week to week or month to month may suggest a relationship to exposure to the drug being monitored. Such a signal can be strengthened by comparing the age and sex adjusted relative risks of drug being monitored with these values for comparable drugs already studied by PEM. Eg: gynaecomastia with finasteride

Visual field defects in patients taking vigabatrin
The incidence of hallucination associated with
tramadol

- Gastrointestinal intolerance due acarbose

(Klein & Lippman)

5. Long Latency adverse reactions:

Delayed reactions can be detected by sending out
further questionnaires relating to those patients
shown in the initial PEM Survey to be receiving
long-term medication.

E.g. long term lamotrigine in epilepsy.

6. Investigation of disease:

The PEM database provides a valuable opportunity
to study disease as well as drugs.

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.

Record Linkage System

◦ 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 error 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 enrolment file stores demographic

information, date of birth, gender, place and type of employment, and benefit package, as well as linkage to dates of enrolment and disenrollment. A unique identifier is assigned to each member at the time of enrolment 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. inpatient, hospital outpatient, emergency room, surgery centre, physician's 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 the pharmacy 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 identification number is assigned to each health professional and institution.

Precautions are taken to protect the identity of 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 (7-8 months).

Applications:

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

• Data sources can be examined to eliminate duplicate records, to identify underreporting and missing cases (e.g. census population counts), to create person-oriented health statistics and to generate disease registries and health surveillance systems. Some cancer registries link various data sources (e.g. hospital admissions, pathology and clinical reports, and death registrations) to generate their registries.

• Record linkage is also used to create health indicators. For eg. fetal and infant mortality is a 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 data, such as 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, or 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.