IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

# A Review on Post approval Drug Safety Surveilliance

## 1. Introduction

As the name implies, the post-market surveillance entails the monitoring of the medical device once it hits the market. Because of a history of manufacturers' negligence toward this aspect of risk assessment, the FDA has put forth requirements and regulations for manufacturers to follow after devices have become available for sale. These include the use of tracking systems, reporting of device malfunctions, serious injuries, or deaths that the device may have caused, and registration of the organizations that produce or distribute the respective device. Post-market surveillance specifically falls under section 522 of the act. Other post-market requirement includes post-approval studies that are usually carried out during a premarket approval, humanitarian device exemption, or product development protocol application.

Noncompliance with the post-market surveillance standards are may cause the manufacturer to incur large legal fines are loss of license, or even imprisonment. The importance of the post-market surveillance lies in the fact that it allows the manufacturers to rapidly identify any problems in their device and solve them before it affects more people. Outsourcing of post-market surveillance is also a common practice among the companies to ensure that they meet all the requirements and that their product is safe for its users. Since most manufacturers' products are sold in around the world it is important that they practice compliance according to each country's guidelines. It is natural that they may impose challenges sometimes but they should be followed as user safety is the priority.

Although premarketing clinical trials are required for all new drugs before they are approved for marketing, with the use of any medication comes the possibility of adverse drug reactions (ADRs) that may not be detected in the highly selected populations recruited into randomized clinical trials. A primary aim in pharmacovigilance is the timely detection of either new ADRs or a relevant change in the frequency of ADRs that are already known to be associated with a certain drug that may only be detected in more typical clinical populations because of their greater range of illness severity and more comorbid illness and use of other medications.

Moreover, less common ADRs will require larger populations to be detected. Historically, pharmacovigilance relied on case studies such as the Yellow Card system in Britain and case control studies, The Uppsala monitoring center reports and classic Venning publications also highlighted the importance of individual case reports for signal detection. More recently, several large-scale post-marketing studies have been designed to detect ADRs. However, these studies are often unrepresentative of the potential users of a drug, have incomplete data, have short follow-up, and have inadequate sample size for rare ADRs.

Furthermore, a control group i.e., patients suffering from same disease but undergoing no active treatment) is often unattainable except in very special circumstances. In the following sections, we review a variety of approaches for studying ADRs ranging from spontaneous reports to ecological studies to analyses of medical claims databases. Our review focuses on both design and analytic issues, highlights strengths and limitations.

Next, we consider meta-analysis of randomized controlled trials. This is a favorite approach of the psychopharmacological division of the U.S. Food and Drug Administration (FDA) and involves pooling information from multiple randomized controlled trials. This is a favorite typically placebo controlled. Small sample sizes consisting of patients monitored for short time periods, and ascertainment biases that are associated with a focus on spontaneously reported AEs. Finally, we review various approaches to the design and analysis of studies that are based on large-scale medical claims databases. Medical claims data are often based on large enough samples to evaluate all but the rarest AEs.

The limitation is that these studies are not randomized; therefore, results can be biased owing to factors such as confounding by indication, in which patient characteristics lead to treatment of a particular type and it becomes difficult to disentangle the effects of treatment from the characteristics of the patients that lead to treatment. General Considerations for Effective Post-Marketing Surveillance Legal Mandate, Governance, Financing, Human Resources and Capacity, Management and Planning, Sampling and Testing, Coordination and Communication, Sustainability Ensuring that a post-marketing surveillance programme.

## 2. Definitions

### ➢ Pharmacovigilance:

Pharmacovigilance is defined by the World Health Organization (WHO) as 'the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem.[1]

### ➢ An adverse drug event:

An Adverse Drug Event is "an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug adverse drug reactions and overdoses and harm from the use of the drug (including dose reductions and discontinuations of drug therapy Adverse Drug Events may results from medication errors but most do not.[2]

### ➢ Adverse drug reaction:

An Adverse Drug Reaction is a "response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function." Note that there is a causal link between a drug and an adverse drug reaction.[2]

### ➢ Post approval drug safety surveillance

Post Approval Dug Safety Surveillance (PMS), also known as post market surveillance, is the practice of monitoring the safety of a pharmaceutical drug after it has been released on the market and is an important part of the science of pharmacovigilance. Since drugs and medical devices are approved on the basis of clinical trials, which involve relatively small numbers of people who have been selected for this purpose meaning that they normally do not have other medical conditions which may exist in the general population post-marketing surveillance can further refine, or confirm or deny, the safety of a drug or device after it is used in the general population by large numbers of people who have a wide variety of medical conditions.

## 3. Objectives

- The Post marketing drug safety surveillance system is not a substitute for important premarket information required to support application approval, but rather a means to obtain more information on the safety and effectiveness of the drug after its approval.
- To identify previously unrecognized adverse effects as well as positive effects.
- Differentiate FDA post-market surveillance from device manufacturer surveillance activities manufacturer.
- Identify the components of post-marketing drug safety surveillance
- Introduce risk management as part of PMS
- Determine sources of data.
- Review procedures supporting post-market surveillance.
- Look at trending and analysis.
- Introduce FDA vision for a national post-market surveillance system.
- Summarize how adverse event reports are collected and analysed by FDA/UMC.

## 4. Post Marketing Surveillance and its Role in Design

As stated earlier, all medical drug companies must have an active post-market surveillance system in place. Some think this is only to capture complaints; it is not. The PMS is to capture information about your drug after it has hit the marketplace, be that good, bad, or indifferent. It is common, therefore, to have a three-pronged attack:

- The first prong is to have a clinical lead looking at the clinical literature and knowledge base.
- The second prong is to have the marketing manager collect all information from your sales and marketing staff, and current market literature.
- The third prong lies with the technical director whose job it is to collect all quality related information and material from the technical knowledge base.

The trick is bringing all three prongs into one outcome. Hence all three strands need examining for every one of your main products with a view to coming out with one of the following design outcomes

- New product
- Design modification
- No change

This can only happen if you discuss all three inputs relative to your drug. This need not be every week but it should be more than once a year! A further input is, of course, the emergency input for a design modification of the drug leads to Preventative Action Notice.[2]


**Fig 1: Post marketing surveillance and its role in design**

## 5. Correlation Assessment between ADRs and ADEs

Correlation assessment between ADRs and ADEs was conducted according to method recommended by CFDA evaluation center of adverse reactions. All ADRs/ADEs were preliminarily classified on basis of their definitions, respectively.

- Certain: The sequence between medication and ADRs' occurrence is reasonable. ADRs could be stopped or quickly reduced or turn better after drug withdrawal. Alternatively, ADRs would be occured again or significantly worse when drug was re-administered.

- Probable: There is no history of repeating medication, others are same as "Certain". If the investigated drug was administrated in combination with other drugs, the probability of ADR caused by combined drugs could be excluded.

- Possible: There is close relationship between medication and ADEs' occurrence. It is coincided with common type of ADRs, but there is no reaction data after drug withdrawal, or there are more than one drug leading to ADRs/ADEs, or causative factors of primary disease could not be ruled out.

- Unlikely: There was no close relationship between medication and ADEs' occurrence. The reactions do not link to ADRs/ADEs of the investigated drug. Reactions during development of primary disease may display similar clinical manifestations.

- Pending: There are missing contents of "Monitoring Information Form" and evaluation will not be completed until the supplementary specifications are provided. Thus, it is difficult to determine relationship between cause and effect due to absence in documentation.

- Unassesable: many items in the "Monitoring Information Form" are unavailable. It is unable to analyse relationship between cause and effect because missing items could not be supplemented.[2,17,18]

# 6. Method Design

This study was not a randomized controlled trial but a centralized monitoring study in hospital and all data were collected from clinical daily treatment without any intervention. Thus this study was not designed entirely according to CONSORT guidelines. We designed the monitoring data collection and quality control method according to other hospital centralized monitoring methods.

## 6.1 Method of Monitoring Data Collection

The monitoring data were from two parts: monitoring table and hospital information system / laboratory information management system (HIS/LIS). Information in front page of the medical record, doctor's orders and results of laboratory examination were extracted from HIS/LIS system after being approved by ethics committee. To ensure the safety of the patient's personal information all monitors have been trained on information confidentiality. Monitoring table consists of (basic monitoring information including daily dose, frequency, drug combination, etc.) and (ADR/ADE information). Was filled by pharmacists within 5 days after the end of medication by "face-to-face" observation. Monitoring was filled once ADR/ADE, especially serious ADR/ADE such as anaphylactic shock, severe allergic reactions, severe mucocutaneous lesions, liver damage,

renal damage, and death, was happened. Accordance to requirements of "National ADR Reporting and Monitoring Management Measures", all serious ADRs/ADEs were further investigated by a panel consisting of head of organizer of the project and staffs from sub centre and manufacturing enterprise. "Adverse Drug Reaction / Event Report" was written and submitted to official website according to the rules of the FDA. [13,14,15,16]

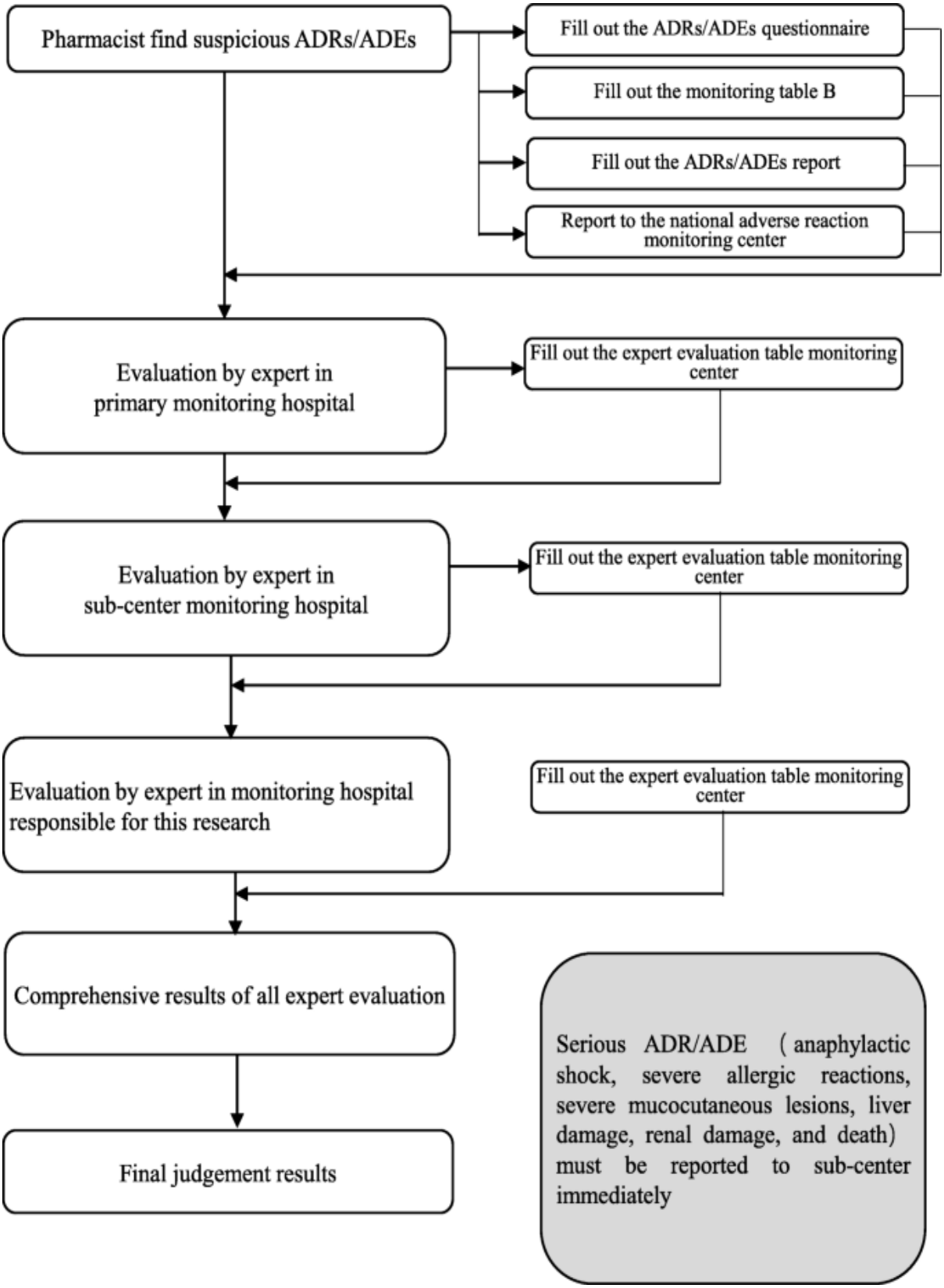


**Fig 2: Method of monitoring data collection**

# 7. Methodology Adopted

| Data source | Experimental strategies | Statistical methodologies | Strengths | Weaknesses |
|---|---|---|---|---|
| Spontaneous reports | Passive Reporting System (FDA) | Proportional Reporting Ratio | Large enough numbers to measure rare adverse events. | Confounding by indication |
| | Active Reporting System (VA) | Bayesian Neural Networks | | Systematic underreporting |
| | | Empirical Bayes screening | | Questionable representativeness |
| | | Multi-Item Gamma Poisson Shrinker | | Publicity bias |
| | | Cumulative Sum | | Extreme duplication |
| | | Random-Effects Poisson Regression | | Unknown population at risk |
| Ecological methods | National rates | Time series methods | Large samples or entire populations can be studied. | Do not know if person experiencing the AE actually took the drug. |
| | Natural experiments | Change-point analyses | Permits between stratum comparisons | Subject to ecological fallacy |
| | Small area estimation | Mixed-Effects Poisson Regression | Hypothesis generation | Geographic variability in reporting |
| Meta analysis | Synthesis of randomized controlled trials | Fixed-Effects model (MH model) | Randomization | Limited generalizability |

| Data source | Experimental strategies | Statistical methodologies | Strengths | Weaknesses |
|---|---|---|---|---|
| | Synthesis of observational studies | Random-Effects model (DL model) | Person-level | Exclusion of zero-event studies |
| | | Mixed-Effects Logistic Regression | | Heterogeniety |
| | | Multilevel mixture models | | Publication bias |
| | | | | Ascertainment bias |
| Medical claims | Case-control studies | Fixed-Effects Logistic and Poisson | Large samples | Confounding by indication |
| | Cohort studies | Mixed-Effects Logistic and Poisson | Person-level | Confounding by time of treatment |
| | Within-subject designs | Person-time logistic models | Concomitant medications | Unmeasured confounders |
| | Between-subject designs | Propensity scores | Comorbid diagnoses | Unsystematic diagnostic criteria |
| | Matching | | Prior history of relevant AEs | Based on filled prescriptions only |
| | Differential effects | | Generalizable | Limited dosage and duration data |
| | Coherence | | | |

**Table 1: Methodology adopted**

# 8. Spontaneous Reports

Most ADRs are the product of clinician observation or patient self-report. Recently, the World Health Organization (WHO) and the U.S. FDA have used automated methods to mine spontaneous report databases. Modern data mining combines statistics with ideas, tools, and methods from computer science, machine learning, database technology, and other classical data-analytical technologies. In the context of drug safety, the objective is to detect local structures or patterns and to determine if they are inconsistent with chance occurrence. Patterns are usually embedded in a mass of irrelevant data. Interesting patterns can arise from artifacts of the data-recording process or from genuine discoveries about underlying mechanisms. Therefore, deciding whether a pattern is interesting requires knowledge from experts to understand exactly what is being described. The increasing number of large databases maintained by various regulatory agencies and pharmaceutical companies around the world provide the opportunity for some novel exploration in post-approval drug safety.

Several statistical methods have previously been suggested for post-marketing safety surveillance. Haugen & Zhou grouped these methods into two categories: numerator-based methods and denominator-dependent methods; the former category makes no adjustments for the population at risk (e.g., number of prescriptions sold for each drug), whereas the latter category makes direct or indirect adjustments. Spontaneous reporting centres and drug safety research units routinely use various numerator-based methods such as empirical Bayes screening (EBS) (a variant of which is used by the FDA), Bayesian Confidence Propagation Neural Network (BCPNN used by WHO), and proportional reporting ratio (PRR). Denominator-based methods include Cumulative Sum, Time Scan, and Poisson methods. [25],[29]

## 8.1 Proportional Reporting Ratio

Proportional Reporting Ratio (PRR) is the simplest method available for signal detection. Its computational form is similar to well-known Relative Risk calculation for 2 × 2 tables in epidemiology. It is the ratio of the number of reports of a specific AE to all AEs for a particular drug. Of concern is that large numbers of AE reports of a particular kind effectively inflate the denominator for that drug and thereby reduce sensitivity for detecting other signals associated with that drug. PRRs have large numbers of false-positive signals because they provide no adjustment for multiple comparisons.[15]

## 8.2 Bayesian Confidence Propagation Neural Network

Bate and his colleague's developed Bayesian Confidence Propagation (BCPNN), which can handle large data sets and is robust to missing data. It is based on identifying relationships between a drug and AE that differ significantly from the background interrelationship in the database. The information stored as the weights in BCPNN is used for quantifying drug-ADR dependencies. The algorithm computes the information component (IC) and its interval estimates between specific drugs and AEs present on the same report. To detect a signal based on the IC of drug-event association, the analyst performed sequential time scans of the database. An IC with a lower 95% CI > 0 that increases with sequential time scans is the criterion for signal detection.

## 8.3 Empirical Bayes Screening

Empirical Bayes Screening computes the baseline (expected) frequency under a row (drug) and column (event) independence assumption for multiple two-way tables. If the drug and event are independent, the proportional representation of that event for a specified drug should be the same as the proportional representation of that event in the entire database. Three distance measures

(*a*) relative risk,

(*b*) logP, and

(*c*) the geometric mean

of the posterior distribution of the true relative reporting ratio—were used to rank drug-event frequencies according to their magnitude.

The likelihood function assumes each observed count is a draw from a Poisson distribution with varying unknown means with a common prior distribution: a mixture of two gamma distributions. The U.S. FDA currently uses a Multi-Item Gamma Poisson Shrinker, which is a variant of the Gamma Poisson Shrinker (GPS). The MGPS algorithm computes signal scores for pairs and for higher-order combinations of drugs and events that are significantly more frequent than their pair-wise association would predict. [11,27,12,55]

## 8.4 The Cumulative Sum (CUSUM) Method

The Cumulative Sum (CUSUM) method is based on the cumulative sum of differences between observations and their expected values. A signal is detected if the signal statistics exceed the threshold value. The threshold is determined by average run length (ARL) based on the mean and variance of the background incidence. The method requires background comparison time interval and may therefore limit the timely identification of safety problems.[53]

## 8.5 Poisson Method

The Poisson method is a denominator-based method that requires some estimate of the population at risk (e.g., national prescription rates). Gibbons et al. developed a random-effects Poisson regression model for the simultaneous analysis of large numbers of spontaneous reports of possible ADRs. Parameters are estimated using marginal maximum likelihood, and individual drug-AE rate ratios are estimated using either empirical Bayes or parametric or nonparametric full Bayes methods. Confidence (posterior) intervals that do not include 1.0 provide evidence for either significant protective or harmful associations of the drug and the AE. The Veterans Administration (VA) has recently developed an SRS that has denominators based on all outpatient prescriptions, making denominator-based methods even more attractive (F. Cunningham, personal communication). [21]

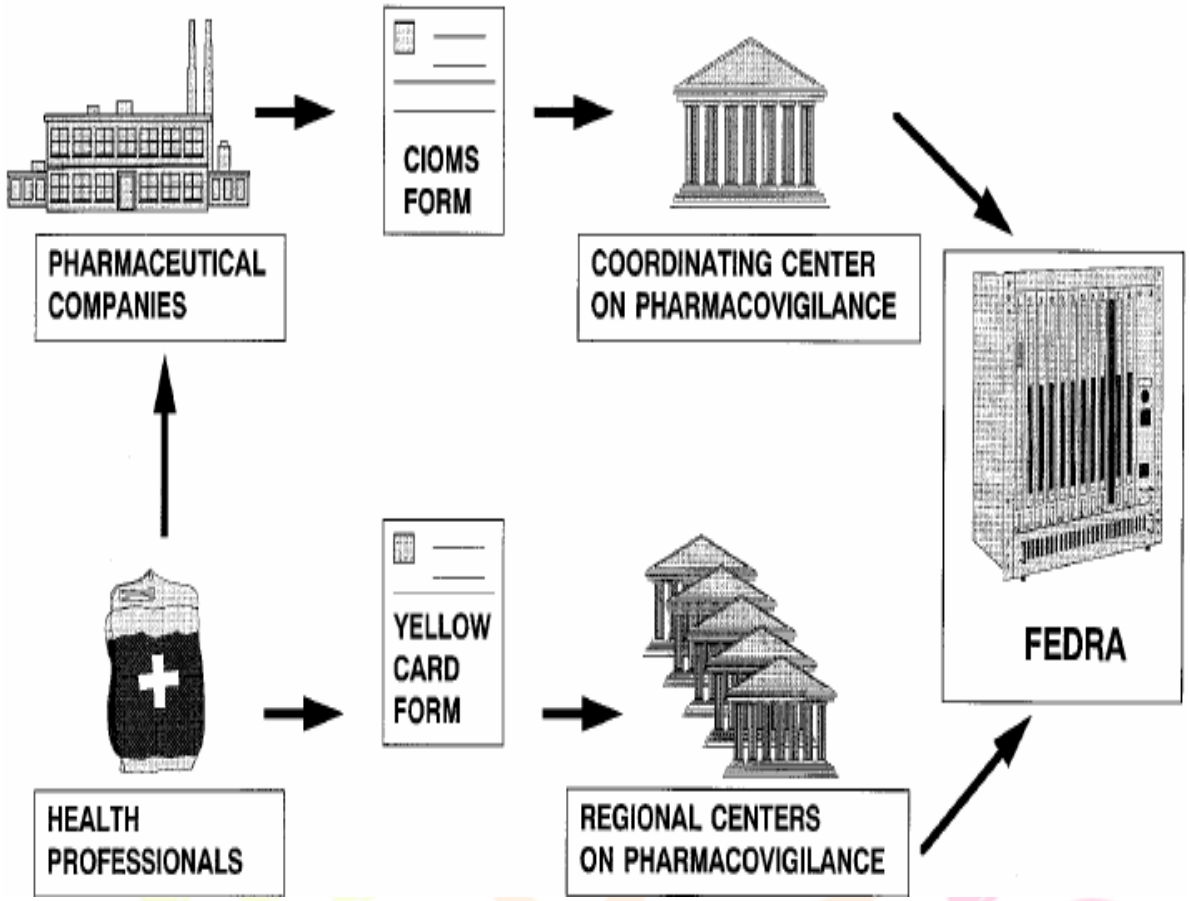


**Fig 3: Showing spontaneous reporting post-marketing drug safety surveillance**

## 8.6 Limitation of Spontaneous Reports

Spontaneous Reports data have numerous limitations.

These include:

(*a*) confounding by indication (i.e., patients taking a particular drug may have a disease that is itself associated with a higher incidence of the AE

(*b*) systematic under-reporting

(*c*) questionable representativeness of patients

(*d*) effects of media publicity on numbers of reports

(*e*) extreme duplication of reports

(*f*) attribution of the event to a single drug when patients may be exposed to multiple drugs.

Also, nearly all the AERS analyses now being used fail to account in some way for the number of prescriptions for each drug. Finally, spontaneous reports do not reliably detect ADRs that occur widely separated in time from the original use of the drug. Nowhere is this more problematic than in detecting the effects of drugs on the fetus or long-term effects such as on malignancy in patients who take immunosuppressant medications or experience pulmonary hypertension and cardiac valvular effects from fenfluramine. These limitations can degrade the capacity for optimal data mining and analysis. Despite these known limitations, these are the data on which regulatory agencies around the world primarily rely for the purpose of post marketing surveillance. Fortunately, other methods can provide useful information that is complementary to that produced using existing methods. In the following sections we discuss alternatives to the use of spontaneous reports for identifying ADRs.[5,28]

## 9. Meta-Analysis of Randomised Controlled

Prior to drug approval and/or release of a new drug, a series of RCTs are conducted that include frequencies of spontaneously reported adverse events. Whereas an individual study typically has an insufficient sample size to detect a statistically significant drug-AE relation, synthesis of data from several trials may provide a more powerful statistical inference. In many cases, the research synthesis is performed using meta-analysis. For example, given concerns about the safety of drug-eluting stents, Stettler et al. conducted a meta-analysis of 38 trials in 18,023 patients comparing sirolimus-eluting stents, paclitaxel-eluting stents, and bare-metal stents. A brief overview of statistical methodologies commonly used in meta-analysis of binary outcomes follows.

It is important to note that owing to variability in:

- Treatment outcomes
- Indication for treatment
- Mode of treatment

meta-analysis is hypothesis generating and does not itself provide a causal inference. [54]

### 9.1 The Mantel-Haenszel Method

The Mantel-Haenszel (MH) method assumes a fixed effect and combines studies using the inverse variance of the study-specific odds ratio to determine the weight given to each study. It was originally developed to analyse odds ratios, but it has been extended to include other measures. The basic idea for a fixed-

effects model involves the calculation of a weighted average of the treatment effect across all the eligible studies. The MH test assumes that the odds ratio is equal across all studies.

### 9.2 DerSimonian & Laird Method

DerSimonian & Laird provide an estimate of the combined effect of multiple trials incorporating heterogeneity across studies. They assume a normal distribution for the treatment effects across studies with common mean θ and variance $\tau^2$. This method provides a simple noniterative way to compute the heterogeneity parameter $\tau^2$ and adjusts the weight given to each study for the estimated heterogeneity across studies. This method is more generalizable than the MH test, which assumes a common effect across all studies. However, a number of simulation studies have shown that the heterogeneity estimate has a large negative bias, leading to a biased estimate of the pooled treatment effect, as well. In addition, the Q statistic that is used to test heterogeneity has low power to detect departure from homogeneity. [10,35,50,51,26,37]

### 9.3 Multilevel Mixture Meta Analysis

An extension of the use of random effects in meta-analysis to incorporate heterogeneity of effects across studies is the use of discrete mixtures of random effects. Among other effects, discrete mixtures of random effects can capture multimodality of intervention effects, which may be harmful in some circumstances and beneficial in other contexts or vary over time.[7]

## 10. Medical Claims Data

The use of medical claims data for post-marketing drug surveillance offers several advantages. First, medical claims represent person-level data, similar to RCTs and spontaneous reports, but unlike spontaneous reports, we know the population at risk. Second, several medical claims databases such as the VA or Phar Metrics databases contain longitudinal information on AEs, concomitant medications, and comorbid diagnoses both before and after the drug exposure. Third, the populations that can be sampled are often large enough to study even the rarest of events. Their primary limitation is that they are observational, and any association identified may or may not represent a causal link between the drug and the AE because of potential unmeasured confounding. The primary objective is to design an observational study such that many of the benefits of a RCT are preserved.

### 10.1 Cohort Studies

A cohort study identifies a sample from a well-defined population according to predetermined criteria. In drug surveillance, investigators use two general approaches to conduct a cohort study. The cohort can be

defined in terms of an illness (e.g., cardiovascular disease) or based on an exposure: for example, all patients taking a particular drug, both within a given timeframe. In some cases, we may wish to identify new cases of an illness or an exposure in patients who have neither been diagnosed with the illness nor treated for the illness for quite some time (e.g., several years). This strategy works well for databases with long-term enrollment patterns such as the VA but may be less ideal for managed-care databases where patients may not be continuously enrolled for long enough periods of time. In this case, the cohort study can be designed to have a fixed time window before and after the indication (either diagnostic date or first treatment date), for example, a period of one year before and after the indication. The primary advantage of collecting data before and after diagnosis or drug exposure is that we can evaluate the rate of the AE both before and after the start of treatment.

## 10.2 Propensity Score Matching

Propensity score matching provides a way to balance cases (treated) and controls when numerous potential confounders have been measured. The first step is to develop a model for the probability of being treated with a certain drug (i.e., the propensity score) based on all measured confounders. Then, matching on the propensity score rather than on each confounder can provide balance between the groups, leading to between-group comparisons with greatly reduced bias. Equally important, matching on the propensity score can also identify the presence of bias that is inherent in the particular between-group comparison of interest that cannot be controlled through simple adjustment. For example, in the now-classic example of relationship between smoking and mortality, pipe smoking is seen to have the highest risk of mortality, not cigarette smoking. However, pipe smokers were on average older than cigarette smokers, so the actual comparison was potentially between a 30-year-old cigarette smoker and a 70-year-old pipe smoker. Stratification on age produced an unbiased comparison (at least with respect to observed covariates) that showed a clear effect of cigarette smoking on mortality, above that for both cigar and pipe smoking throughout the life cycle. Propensity score matching is therefore a multivariate extension of the single univariate stratification procedure described by Cochran. [44, 9]

## 10.3 A Limitation of Using Propensity Score Matching

A limitation of using propensity score matching in drug surveillance studies is that medical claims data often have limited information regarding potential confounders. Good choices include demographic variables, diagnostic variables, and concomitant medications, as well as comorbidities. In some cases, longitudinal medical records can be used to identify whether there is a history of related AEs prior to exposure to the drug of interest. The key heis to adjust for the severity of illness, which may be related to both the use of the drug and the AE.

### 10.4 Coherence

The term coherence is used both informally and formally, and both formal and informal definitions are relevant in the current context. Informally, we may predict that a treatment will produce several observable associations, and there is coherence if each prediction is checked and confirmed. Formally, we may devise a measure of how much the outcomes of a patient resemble those predicted for the treatment in question and use that measure of coherence as an outcome in the analysis. In drug surveillance, examples of relevant predicted associations are as follows:

1. Suspected drugs should be associated with higher frequency of AEs compared with rates for other treatments.
2. The increase in frequency should occur after, not before, the start of treatment.
3. There should be no corresponding increase in frequency after the start of other pharmacologic or non-pharmacologic (e.g., psychotherapy) treatments that are not directly related to the AE of interest.
4. An AE shortly after the start of treatment is stronger evidence of an effect than an event years later, and an AE shortly before treatment is stronger evidence of confounding by indication than of an AE many years earlier [45,47]

## 11. General Considerations for Effective Post-Marketing Surveillance

### 11.1 Legal Mandate

The legal provisions, regulations, and guidelines that constitute the regulatory framework for implementing national post-marketing surveillance activities must be in place. The law must clearly stipulate the NRA's authority to establish, implement, and periodically update post-marketing surveillance programs. NRAs should consider post-marketing surveillance a key standalone regulatory function with a legal basis in the national laws and regulations and should establish a dedicated post-marketing surveillance department/unit within the NRA. Medicines regulations should promote a shared responsibility for assuring the quality, safety, and efficacy of medicines across procurement agencies, manufacturers, importers, wholesalers, and retailers of medicines. Market authorization holders (MAHs) should be held responsible for products on the market.

### 11.2 Governance

Effective post-marketing surveillance requires good governance mechanisms that are accountable, transparent, responsive, equitable, inclusive, consensus oriented, and effective, and that follow the rule of law. Strong regulations promote good governance and transparency in medicines supply chains. The NRA should have a sound governance structure that promotes an effective organization with clearly defined roles and responsibilities and documented standard operating procedures (SOPs).

## 11.3 Financing

Governments and NRAs should provide adequate resources for the sustainability of post-marketing surveillance activities, including regulations, processes, budegetary provisions, and human and technical resources for the implementation of an effective post-marketing surveillance strategy. Each sampling and testing activity should have an approved protocol with specific objectives, an approved plan, and a budget. The NRA should mobilize the required funds before starting any sampling and testing activity. The regulatory system and the NRA should use a comprehensive risk assessment to optimize the use of limited resources, including financial and human resources, in the areas that need them the most. Risk-based approaches should be used to determine the types of medicines that will be sampled, the sampling locations, the sample size, and the appropriate analytical test to perform. Using risk-based methods can significantly reduce both sampling and testing costs.

## 11.4 Human Resources and Capacity

Qualified and proficient staff with relevant education, training, skills, and experience should be assigned to perform regulatory activities. The duties, functions, responsibilities, necessary competencies (education, training, skill, and experience), and specific policies should be clearly defined and updated as needed. A code of conduct, including management of conflicts of interest, should be shared with and followed by Establishing a Post-Marketing Surveillance Program 09 NRA staff and external experts. Capacity development is critical in making postmarketing surveillance sustainable and, as such, a training plan for staff should be developed, implemented, and updated periodically. Field-level staff should also be trained appropriately by the NRA and/or NQCL to perform field-level visual inspection or testing of medicines. Finally, medicines quality and post-marketing surveillance topics should be incorporated in relevant health-related training programs, including those for pharmacy, laboratory, and regulatory affairs.

## 11.5 Management and Planning

National post-marketing surveillance activities should be planned and executed annually, using a risk-based approach to determine sampling and testing priorities across different medical products in the public, private, and informal medicines supply chains. Postmarketing surveillance activities should also include public reporting of suspected substandard and falsified medical products, handling of market complaints, control of promotion of pharmaceutical products, detection of medicines, removal and disposal of defective and noncompliant medical products from the market, and implementation of corrective and preventive actions.

### 11.6 Sampling and Testing

Based on the post-marketing surveillance objectives, prioritized according to a country's specific needs, sampling and testing should be conducted using well-defined methodology that is effective and can be rationalized. Riskbased sampling methods should be used to target activities to areas and medicines that are most vulnerable and represent the greatest risk to public health. Similarly, resources should be optimized by using tiered approaches to testing.

### 11.7 Co-ordination and Communication

To implement effective post-marketing surveillance programs and activities, NRAs must coordinate closely with all stakeholders involved directly or indirectly with medicines manufacturing, importation, exportation, and wholesale, and also relevant NGOs donors, and other partners. For each sampling and testing activity, coordination with relevant stakeholders should lead to establishing a plan with well-defined roles and responsibilities for all parties involved. The plan should cover all post-marketing surveillance activities: sampling, testing, data analysis, data reporting, and follow-up actions. Mechanisms should be in place to ensure in involvement and the communication among relevant stakeholders and the various departments/units within the NRA. Similarly, the NRA should hold public consultations during the development or revision of regulations and guidelines relevant to the national post-marketing surveillance program. Published regulations and guidelines should be made available to all stakeholders after publication. Similarly, post-marketing surveillance activities should be communicated within departments of the NRA (e.g., laboratory, inspection, and enforcement) and among relevant stakeholders, countries, and international organizations as appropriate.

## 12. Discussion

PMS is practiced in the form of the Yellow Card scheme that is jointly operated by the MHRA and the Committee of Human Medicines (CHM). The Yellow Card scheme is credited as being one of the first PV schemes aimed at mitigating ADRs.

PMS encompasses the following objectives:

- Monitoring the use of medicines in everyday practice with the aim to identify erstwhile unrecognized ADRs and also changes in the patterns of adverse effects.
- Carrying out risk–benefit analysis for medicines and suggesting suitable actions, if and when necessitated.
- Providing regular updates to healthcare professionals and patients with regard to the safe and efficacious use of medicines.[1,2]

## 13. Outcomes

Pharmacovigilance has clear, well-established goals: to detect ADRs associated with the use of drugs as early as possible, and to avoid risks that may outweigh the benefits of the medication. The evolution of pharmacovigilance has been a slow and steady one. From individual doctors noticing unusual effects in patients and sharing their findings with colleagues to the methods used today to monitor a drug after its release into the market, including spontaneous reports, risk management plans, pro-spective safety studies, and registries.50The main focus of pharmacovigilance has been to detect rare ADRs while giving less attention to the common ones.

Recently, however, there has been a climate of change and efforts are now being made to focus on patient-centered pharmacovigilance rather than population-based and regulation-based pharmacovigilance. A study was conducted to evaluate the different aspects of pharmacovigilance currently, and in the future. The study claimed that there are developments within the field of pharmacovigilance, including the setting of rules and regulations, as well as the scientific-related issues. Specifically, the study mentioned details regarding those two aspects by stating that: On a regulatory level, these include conditional approval and risk management plans; on a scientific level, transparency and enhanced patient involvement are two important elements. Overall, these new developments will guarantee continuous progress in pharmacovigilance.[24,57]

## 14. Conclusion

To strengthen the spontaneous reporting programs as an effective post marketing surveillance method, more awareness among health professionals and innovative strategies is needed. Integrating pharmacogenetic data can be potential aspect of future pharmacovigilance. To strengthen medicine safety monitoring and reporting by healthcare professionals, more awareness among health professionals and innovative strategies are needed. Integrating the genetic data of patients can be beneficial in predicting adverse effects, therefore avoiding them and enhancing safe prescribing and dispensing by healthcare professionals.

## 15. Result

Though beneficial, spontaneous reporting programs encounter several limitations and difficulties in diagnosing adverse drug reaction. Under-reporting and bias are major challenges. Online signal detection tools and innovative methods are needed to strengthen the spontaneous reporting programs. We provide the various issues to be considered while depending on spontaneous reporting programs as a method of post marketing surveillance. reporting of adverse effects by healthcare professionals who deal with patient lacks clarity in diagnosing the adverse effects. Under-reporting and bias are the major challenges. Online software is needed to strengthen reporting by healthcare professionals. We list the various issues to be considered while depending on healthcare professionals' reporting of adverse effects as a method of post marketing surveillance.

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