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Latest Trends on Case Processing In Pharmacovigilance: Review Article

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Abstract:
Case processing is a systematic procedure that involves receiving information and duplicate check, reporting the case, triage, data entry & narrative writing, quality review, medical review, case closure, reporting ICSRs. Recent advancements in PV include reporting, cloud based global database of ADRs, big data management, data analytics, and artificial intelligence led to fast accessibility to ADRs reporting and management. Thanks to advancements in technology, we are brought closer to a future with less and less deaths from preventable ADRs.

Keywords: *case processing, signal detection, big data, adverse events, adverse reaction, AI, data analytics, ICSR*

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I. Introduction:

Case processing is a systematic procedure that involves receiving information, case entry, duplicate check, reporting the case, triage, data entry & narrative writing, medical review, case closure and reporting ICSRs and aggregate.

Fig. No: 1 representing the systematic pattern of case processing in Pharmacovigilance.

Case receipt:
Initial receipt of cases will take place by electronic systems like E-Mail, FAX, Telephone and social media.

Data verification and validity check Validity assessment:

After receiving the source document (via email, fax, or phone), the case processor will look for the minimum information which is required for a valid safety report, i.e., an identifiable patient, an identifiable reporter, an adverse event/reaction, and a suspect or interacting drug.

Triage:

Under this step, the case processor prioritizes all the incoming reports as per the receipt date, seriousness, causality, and expectedness assessment in the triage step. Once the cases are triaged, they can be processed as per the priority assigned to each case.

This is done to ensure that cases which need expedited reporting can be processed and submitted to the regulatory authorities within timelines.

Duplicate search:

Every safety database has a facility to identify and delete duplicates. The case processor performs duplicate search for every document received with certain characteristics of a case (gender, age or date of birth, reaction, clinical trial protocol, country, reference number, etc.) to identify whether the same report has been data based previously or not. This action is of significance for further processing of the case. The duplicate could actually be follow-up information that could alter the seriousness and hence reporting timeline of the case.[1] Missed duplicates could send misleading information to the signal detection system.

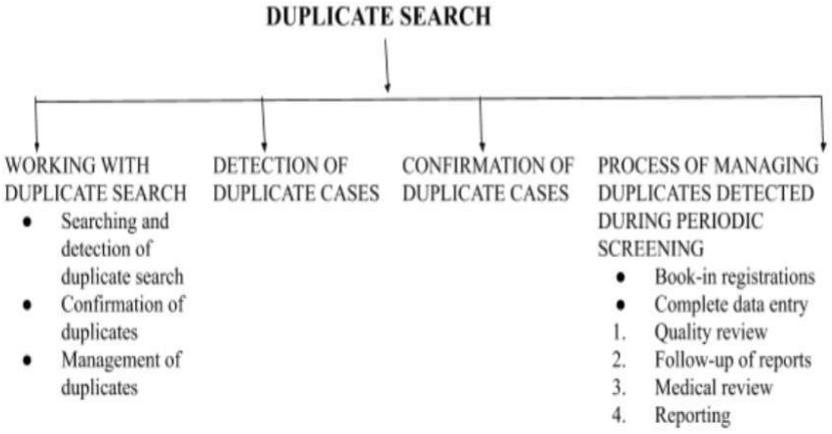

Fig No: 2 Methodology involved in duplicate search

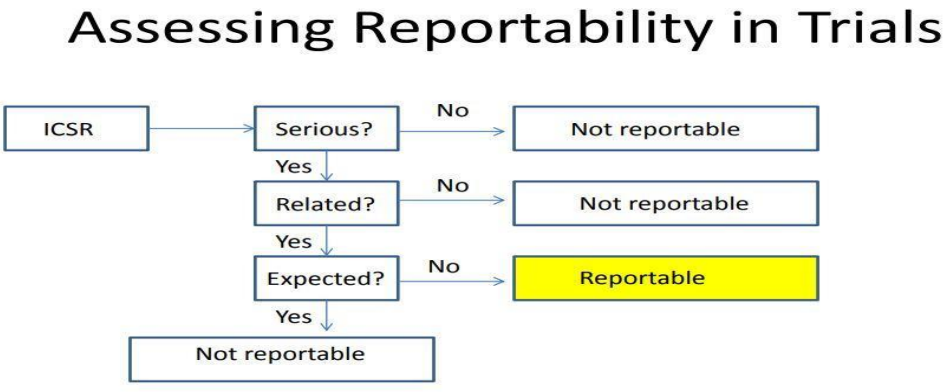

Fig. No: 3 representing the flow chart of assessing reportability in trials

SOURCE OF CASES:

Cases are collected from different sources which includes Clinical trials, Investigator initiated trials (IIT), Post authorization safety studies (PASS), spontaneous cases, observational studies, literature, patient orient programme (POP), Regulatory authorities and Internet-Social media.

LATEST TRENDS IN CASE-PROCESSING:

Cloud based reporting to bring a robust global database of ADRs:

Cloud-based safety database systems now offer state-of-the-art capabilities for handling product safety data. Additional benefits for cloud-based safety databases includes Hardware maintenance and data back-up managed by the cloud provider, security, through a designated enterprise and encryption, facilitation of electronic workflows; ease of direct access to data and ability to collaborate, rapid scalability, availability of systems upgrades, multiple standard reports/outputs.

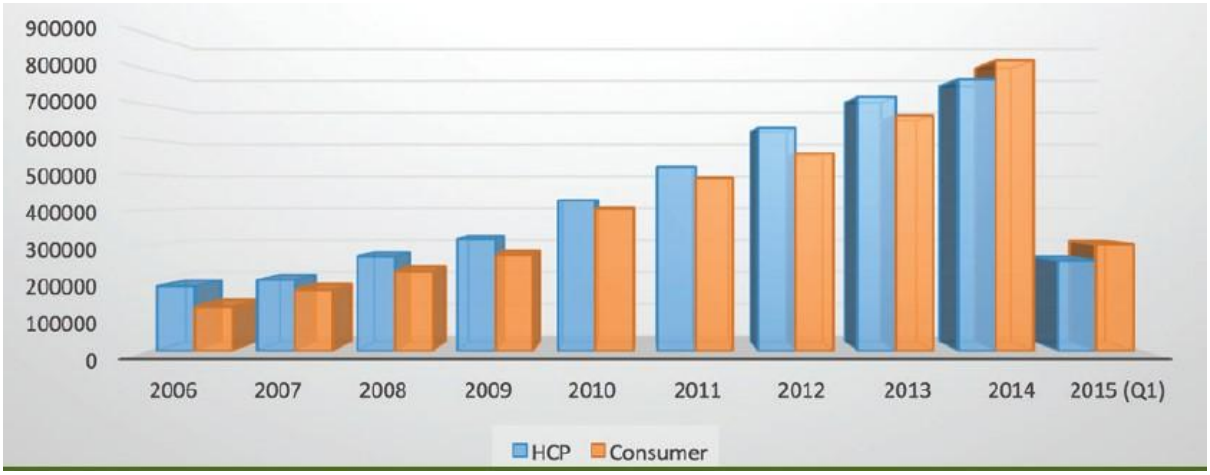

Fig. No: Graphical differentiation of Cloud Database in HCP reports vs consumer reports

To fully realize the capabilities and efficiencies from a cloud-based safety database, implementation of a cloud-based safety database involves careful planning. The following steps should be considered, at a minimum:

Define system requirements: Although cloud-based safety databases provide standard capabilities to store and report data, there are multiple decision points and workflow options to consider to fully utilize the safety database, such as whether to implement electronic reporting through a gateway to regulatory agencies, what ad-hoc reports will be needed or whether to link the safety database to EDC systems being utilized for data capture. Functional requirements generally include interface, business, regulatory, and security requirements. Examples of these database requirements include the ability to continuously monitor the safety data (minimal downtime); accessibility from within offices and remote locations; compliance with country specific regulatory requirements (electronic records, with audit trails and security); acceptance of various types of data (both serious and non serious adverse events, potentially with drugs, biologics, medical devices); generation of various types of outputs including Form FDA 3500A (MedWatch), CIOMS I, MEDDEV reports and line listings; an efficient workflow process with defined user roles; and ability to apply standard coding dictionaries and their upgrades, etc.[2]

Lead the safety database changes: Adopting a cloud-based safety database requires a joint effort between the vendor and the company. Experience dictates that it is critical for a designated lead to be assigned within the company to manage and direct the internal project team. The adoption of the project team approach with members having the appropriate experience and defined roles allows work on multiple, concurrent work streams to be undertaken and helps ensure the project deliverables remain on track. The designated lead also keeps internal management updated on project progress, milestones, etc., and, where appropriate, the financial health of the project.

Integrate updates into standard procedures: A new safety database, especially involving a revised workflow, will usually require updates to existing procedures. Performance of a gap analysis will identify where changes are required. New procedures introduced as a result of the gap analysis, or if system capabilities are expanded, may also be required. The goal should be to utilize an electronic workflow as much as possible and to fully utilize system capabilities within the safety database. Specification of the new and/or updated processes within standard operating procedures (SOPs) will ensure a standardized approach and facilitate training.[2]

Validate the new workflow/system capabilities: Safety database systems require careful validation, in compliance with 21 CFR Part 11, and testing. Each company needs to have standard operating procedures that define the validation process and responsibilities. Use of a cloud based safety database from a commercial vendor generally is less complex than company-hosted systems, but the company needs to have a documented supplier assessment to assess vendor procedures, security, and data integrity, and to determine whether the

vendor's life-cycle management activities can be leveraged to reduce sections of the full validation activities, specifically with respect to installation qualification.

Ensure robust training: Optimal use of the safety database depends on users to enter data consistently and correctly, and this requires training on such topics as data entry conventions, medical coding, workflow management, and quality control. Managers also benefit from training on the available standard reports and data outputs used in expedited and periodic safety reporting, etc. Safety database administrators require training in additional areas such as enterprise setup, granting and revoking user access, data exports, ad hoc reporting, and case/ project closure.

Review key performance indicators To measure the performance with the pharmacovigilance function, key performance indicators (KPIs) or service level agreements (SLAs) should be defined and measured at routine intervals. The best KPIs/SLAs are meaningful and will result in change if outside the target range. KPIs should also be objective, quantifiable, and easily measured. Pharmacovigilance KPIs commonly assess that defined processing and/or reporting safety timelines are met.

Seek continual improvement with adjustments and refinements: As with any set of processes, it is helpful to request feedback and to seek improvements that will reduce cycle times, improve quality and efficiency. Tracking of incident or system help tickets can constitute a source of information for potential improvements. Some improvements may be rapidly implemented if procedural revisions and/or re-education is involved. Others involving change control and retesting/validation may be longer term projects.

Big data to protect and assimilate huge amounts of information:

The pharmacovigilance industry will become more dependent on big data technology for end-to-end assimilation of information as well as ensuring data integrity and security of the data. The importance of big data doesn't revolve around how much data you have, but what you do with it. You can take data from any source and analyze it to find answers that enable[8] 1) cost reductions, 2) time reductions, 3) new product development and optimized offerings, and 4) smart decision making. When you combine big data with high-powered analytics, you can accomplish business-related tasks such as: Determining root causes of failures, issues and defects in near-real time. Generating coupons at the point of sale based on the customer's buying habits.[9] Recalculating entire risk portfolios in minutes. Detecting fraudulent behaviour before it affects your organization.[3]

HADOOP:

HADOOP is an implementation framework for Big Data which is developed in Java. This uses MapReduce programming technique in a distributed computing environment. Google developed HADOOP with MapReduce concept. Hadoop is a platform that provides both distributed store computational capabilities. Apache HADOOP system has got HADOOP kernel, MapReduce, HDFS and a number of various components like Apache Hive, Base and Zookeeper. Hadoop provides the capacity of running business applications with high volume data without interruption by having more than one data node in transferring data in a faster manner.

Architecture Hadoop is a distributed master–slave architecture that consists of the Hadoop Distributed File System (HDFS) for storage and the MapReduce programming framework for computational capabilities. The HDFS stores data on the computing nodes providing a very high aggregate bandwidth across the cluster traits inherent to HADOOP are data partitioning and parallel computation of large datasets. The scalability is high in terms of storage and data processing with the ability of adding additional resources like data nodes. Hadoop has a fault tolerance storage system named Hadoop Distributed File System (HDFS) which could store huge amounts of data using multiple data nodes and survive data failure in data storage by storing data as multiple blocks in multiple nodes.

Below Figure describes the Hadoop architecture. Hadoop will continue to work with alternate nodes available if failure happens in one node so that the user will not get interrupted. Data would be replicated on each data node to maintain the data availability in case of failure. Benefits of HADOOP over big data includes resilience, scalability, low cost, speed and data diversity.[4]

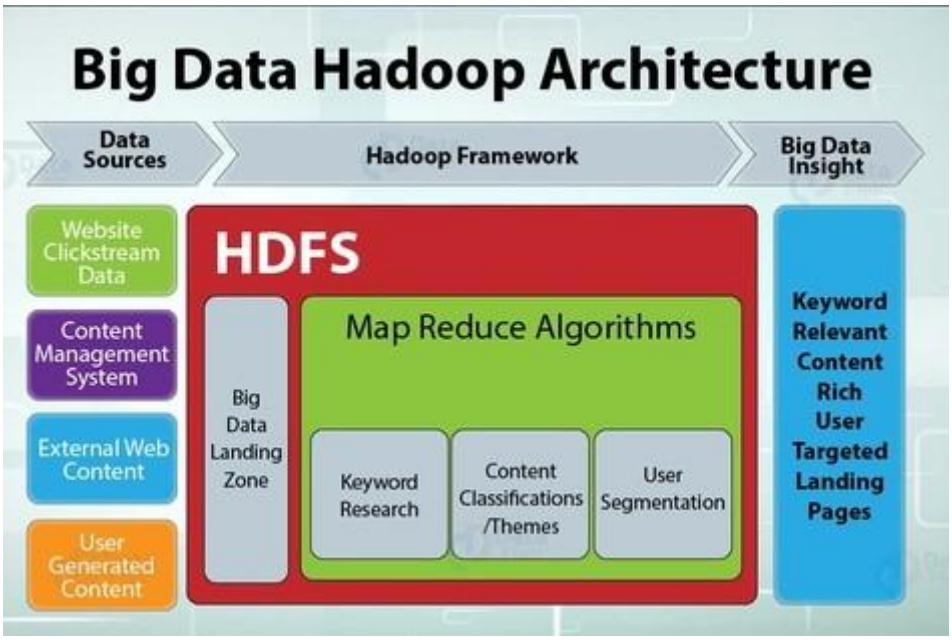

Fig. No: 05 Big data HADOOP architecture

Data analytics to mine insights:

Applying data analytics in pharmacovigilance processes increases the speed of signal detection which essentially seeks information that point to casual relationships between drugs and reported adverse or beneficial events. Data mining is the process of discovering patterns in large data sets involving methods at the intersection of machine learning, statistics, and database systems. Data mining is the analysis step of the "knowledge discovery in databases" process or KDD.

Purpose of Pharmacovigilance Analytics:

Our purpose should be to establish a PV data analytics process designed to leverage big data and the benefits of using such data across the value chain to build synergy between traditional (including regulatory obligations) analytics and big data analytics to provide faster and better insights to the organization. Pharmacovigilance analytics serves as one of the instruments for the continuous monitoring of pharmacovigilance data. All available evidence on the benefit-risk balance of medicinal products and all their relevant aspects should be sought. All new information that could have an impact on the benefit-risk balance and the use of a product should be considered for decision making. PV analytics should be applied to gain insights by integrating data related to medicinal products from multiple sources and applying techniques to search, compare, and summarize them.

OVERVIEW OF PHARMACOVIGILANCE ANALYTICS:

Pharmacovigilance departments must have in place the ability to quickly identify risks based on internal and external information, through processes that identify and extract product and indication-specific information from across the organization.

PV analytics will be used for, but not limited to:

Monitoring of compliance regarding AE / case management. Supporting analysis for signal detection. Contributing to the elaboration of benefit-risk assessments (as stand-alone, or as part of regulatory aggregate reports) and providing knowledge discovery on the factors governing the association between the exposure to a medicinal product and its effects on the population.[5]

SIGNAL DETECTION:

Signal detection and its assessment is the most important aspect in pharmacovigilance which plays a key role in ensuring that patients receive safe drugs. For detection of adverse drug reactions, clinical trials usually provide limited information as they are conducted under strictly controlled conditions. The current method of detecting a signal is predominantly based on spontaneous reporting, which is mainly helpful in detecting type B adverse effects and unusual type- A adverse effects. Other sources of signals detection are prescription event monitoring, case control surveillance and follow up studies. Signal assessment is mainly performed by using Upsala Monitoring scale & Naranjo scale of probability to analyze the cause and effect analysis.

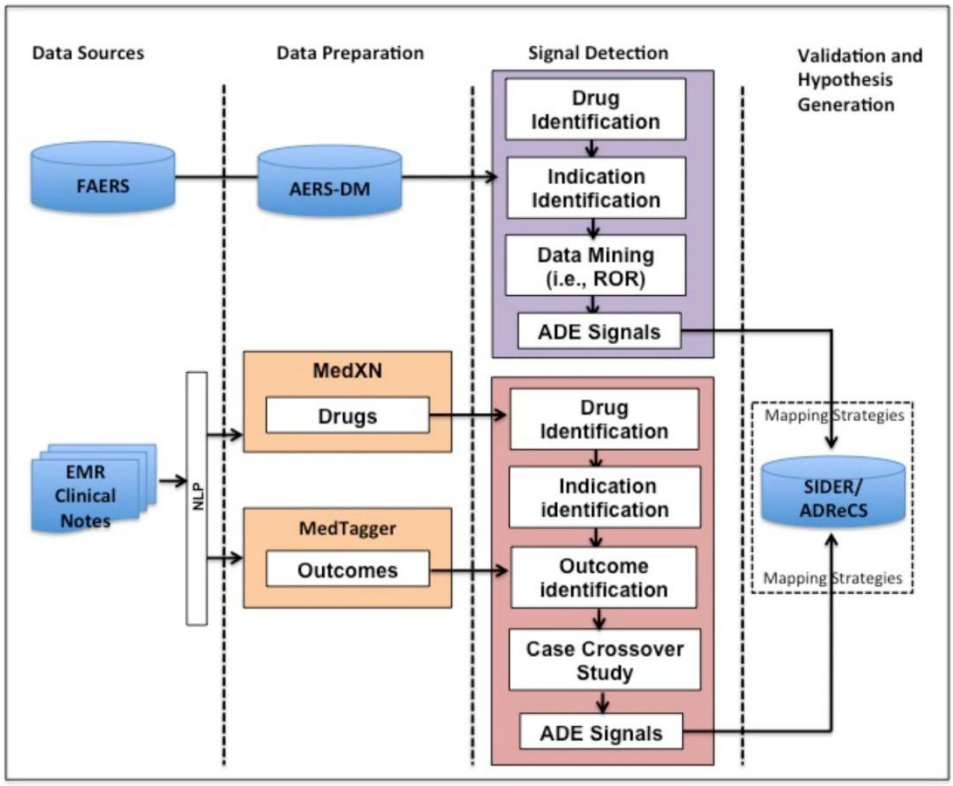

Fig. No: 06 Flow chart explaining Signal detection Process

Signal detection and their assessment is a very vital and complex process. The early detection of safety signals as soon as possible is increasingly important and of great interest to the pharmaceutical industry, regulators, and the public domain. Signals have both qualitative and quantitative aspects. Different categories of adverse events need different methodologies for detection. The primary function of pharmacovigilance is early detection of signals. In the 1960s, thalidomide tragedy occurred due to late signal detection. However, spontaneous reporting systems have now been developed and used all around the world. The safety signals are generated by various sources such as spontaneous reporting, case control and cohort studies, pre-clinical as well as clinical studies as shown in Fig.

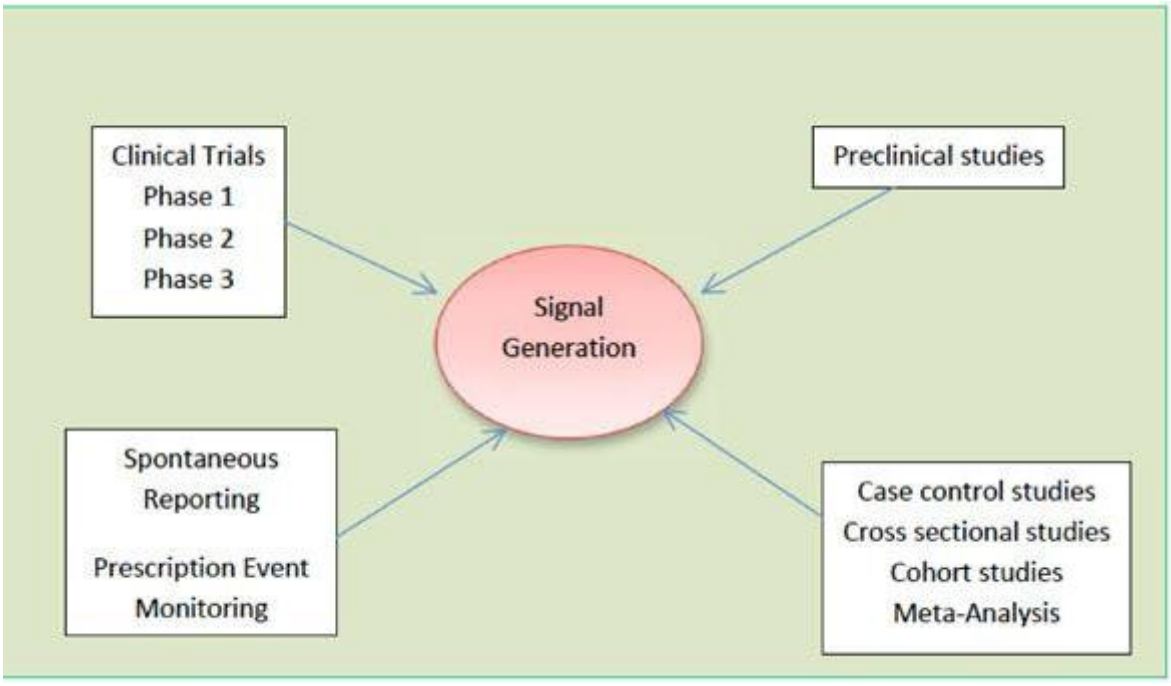

Fig. No: 07 Signal generation procedures

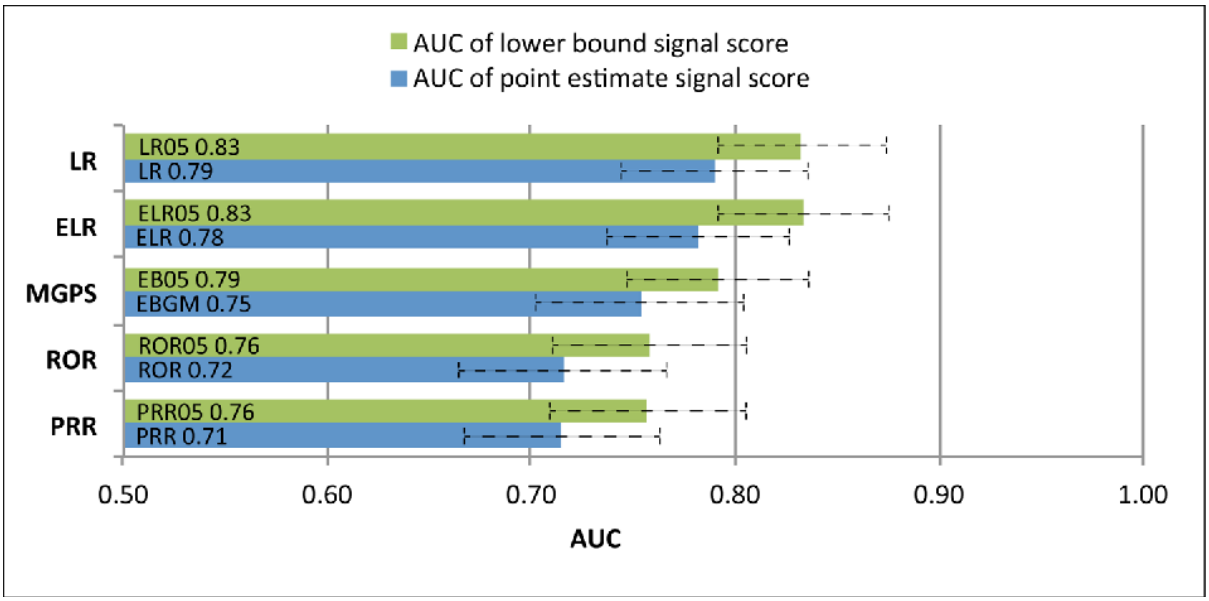

Fig. No: 08 example of graph representing performance of Pharmacovigilance signal-detection algorithms

QUALITY ASSESSMENT:

The signals with incomplete information that might make the causality assessment impossible or of no use are excluded. The subjective assessment of the quality of the reports is mainly based on the patient and drug information. Patient information includes completeness of information with- patient initials, age, sex, date of birth (DOB), weight, diagnosis for which the medications were being taken, relevant history, adverse event description, adequate description of the event, when did the event occur? When did the event subside? How the event was managed? What was the outcome? Whether the event abated on stopping the drug or reducing the dose of the drug? Whether the event reappeared on reintroduction? Any supportive laboratory data? Drug information includes suspected medication with their brand name and/or generic name, labelled strength, manufacture, dose used, frequency of use, route used and therapy dates, concomitant medications including self-medication and herbal remedies *etc.*[10,11]

CODING OF ADVERSE DRUG REACTIONS:

Medical coding is the process of transforming descriptions of ADRs into universal medical terms with the help of drug dictionaries such as MedDRA, WHO-ART, WHO-DDE, CONSTART, ICD10 CM. Med DRA is clinically validated international medical terminology used by the regulatory authorities and the regulated bio pharmaceutical industries throughout the entire regulatory process, from pre- marketing to post-marketing activities & for data entry, retrieval, evaluation & presentation. WHO-ART (World Health Organization adverse reactions terminology) is maintained by UMC and is used for coding clinical information in relation to the drug therapy. WHO-DDE (World Health Organization Drug-Dictionary Enhanced)is used for the classification of drugs providing proprietary and non-proprietary names of medical products used in different countries, together with all active ingredients. COSTART (Coding symbols for thesaurus of adverse reactions terms) was developed by the United States Food and Drug Administration (FDA) for the coding, filing and retrieving of post-marketing adverse reaction reports. ICD9CM (International classification of diseases 9-revision clinical modification) is also used for coding of ADRs.[12]

Country	**Regulatory agency**	**Data base**	**ADR forms**
USA	FDA	AERS	Med Watch
Europe	EMEA	EudraVigilance	-
UK	MHRA	-	Yellow Card
India	CDSCO	Vigiflow	Suspected Adverse Drug Reaction Forms
Japan	PMDA	-	-

Australia	TGA	-	Blue Card
Singapore	HAS	-	ADR Watch
Canada	HC	Canada Vigilance	Canada Vigilance Reporting Form
Malaysia	NPCB	-	-
Saudi Arabia	SFDA	-	-
Brazil	ANVISA	-	-

Table no 5: Databases of different countries

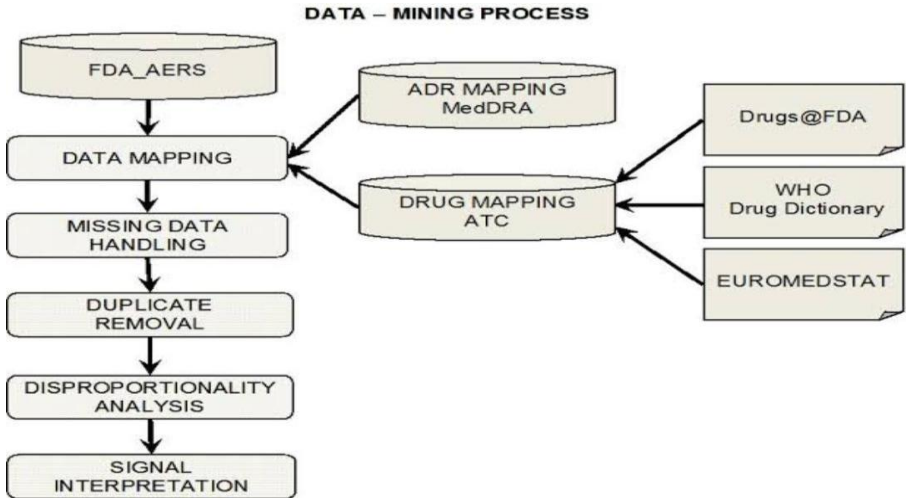

Fig no: 09 Flow chart on Data Mining Process

Data Sources and Statistical Data Mining Methods used in Safety Signal Detection:

From all these statistical methods, generally used methods are proportional reporting ratio and Bayesian method. Of these two, proportional reporting ratio is an easy and convenient method which is used for particular one drug–event signal detection from spontaneous reports. The Bayesian method is used when more combinations are used. It is limited when there is a small number of data available. [13]

Proportional reporting ratio (PRR)

Proportional reporting ratio method which can be easily used for periodic signal detection. The PRR is a statistical method used to detect SDRs in pharmacovigilance databases such as EudraVigilance. This method relies on the principle that when a Signal of Disproportionate Reporting (involving a particular adverse event) is identified for a medicinal product (referred to medicinal product P), this adverse event is reported relatively more frequently in association with this medicinal product P than with other medicinal products. This relative increase in the adverse event reporting for the medicinal product P is reflected in a table based on the total number of individual cases contained in a pharmacovigilance database, as follows:

The general criteria to run the PRR are as follows:

The value A indicates the number of individual cases with the suspect medicinal product (P) involving an adverse event R. The value B indicates the number of individual cases related to the suspect medicinal product P, involving any other adverse events but R. The value C indicates the number of individual cases involving event R in relation to any other medicinal products but P. The value D indicates the number of individual cases involving any other adverse events but R and any other medicinal products but P.

The PRR is computed as follows:

PRR = [A/(A+B)]/[C/(C+D)]

Example: Proportion of individual cases of nausea involving a medicinal product 'Trade Name'= 5% (e.g. 5 reports of nausea amongst a total of 100 reports reported with medicinal product 'Trade Name'). Proportion of reports of nausea involving all the other medicinal products in a database (but medicinal product 'Trade Name') = 5% (e.g. 5000 reports of nausea amongst 100,000 reports reported with all other medicinal products). Therefore, the PRR is equal to 1 (0.05/0.05)

The chi-square (χ2) statistics:

The Chi-square is a statistic, which is traditionally used in dis-proportionality analyses. In certain standard queries of the EudraVigilance Data Analysis System, the Chi-square is used as an alternative measure of association between the medicinal product P and the adverse event R based on the following calculation:

Chi-square = (AD-BC) (A+B+C+D)/(A+B)(C+D)(A+C)(B+D)

For instance, drug-event combinations with at least three reports, a PRR >3 and a chi-square >5 would represent a signal.

PRRs are relatively easy to understand and calculate and are now part of routine surveillance activities so this method has increasing evidentiary support. Computational ease of use is an important advantage considering the dynamic nature of the data and associated sequential scans of increasingly large data sets. Its greatest utility may be in highlighting drug-event combinations with intermediate PRRs, since those with very large scores were noted to involve recognized adverse events (e.g. rifabutin and uveitis), while pairs with PRRs near 1 may be triaged as likely background noise. Care must be taken when strong signals are detected for a given drug, since this will reduce the PRR for other adverse events with that drug. This could be addressed by excluding events with very strong 14 signals.[13]

AGGREGATE REPORTING

Aggregate reports give special importance or value on evaluation of safety which comprises of risk-benefit and do not focus on individual cases. In aggregate reporting, cases are analyzed from various sources at regular time intervals and submitted to respective regulatory authority of the country. The aggregate report examines and summarizes all existing safety experience with a medicinal product. Report includes benefit-risk assessment of Adverse Drug Reaction (ADR) and the Serious Adverse Event (SAE, Pregnancy reports. Pre Approval aggregate report contains Investigational New Drug (IND) report in United States and annual safety report in Europe. The post approval aggregate report is Periodic Benefit Risk Evaluation Report (PBRER), Periodic Adverse Drug Experience Report (PADER), and Periodic Safety Update Report (PSUR).

Periodic Safety Update Report (PSUR)	**Periodic Adverse Drug Experience Report (PADER)**	**Periodic Benefit Risk Evaluation Report (PBRER)**	**Development Safety Update Report (DSUR)**
Regular Periodic safety update reports (PSUR) shall be provided by candidates by a) Report information from a suitable source b) Relates contact of patient information. c) Review the status of market authorisation in various countries. d) The product data should be changed to enhance the use of the product.	They are presented regularly in post-marketing safety reports in the United State PADER should be presented on a periodical basis for the first three years after approval of drug in the United States and annually thereafter.	It emphasizes on benefit-risk evaluation.	It is prevalent for regular reporting or reporting of drugs being marketed under research in the ICH region.

It covers ongoing safety issues and helps marketing authorization holders for conducting the efficient analysis of safety information on a consistent basis. PSUR includes an update on developing or urgent safety issues.	Its Objective is to provide summary data with an assessment of an approved drug product's benefit risk profile. All new data from adequate sources should be reported, such data should be to patient interaction to the medicine, any significant safety-related variations should be reported, opportunities should be created periodically for a comprehensive safety review and changes to the authorized medicine label should be produced to optimize product use.	It provides information on all generics, product licensed in one country only.	It is an annual report, U.S. Investigation New Drug Application (IND) and the EU yearly Safety description is a common standard for periodic reporting on the drug being developed.
This grows very important in order to analyse the product's benefit risk. PSUR should define the studies that are scheduled and performed to study security problems. All dosage form, formulation, indication of new drug should be contained in the single PSUR.	The information obtained from commercial marketing experience, post marketing clinical investigation, a report in scientific literature, the unpublished scientific article should be reviewed by the marketing authorization holder.	All new safety and efficacy evidence should be reported in the appropriate unit of PBRER.	It provides data on promoted drugs under additional study. The outcome of the evaluation is an investigational drugs security profile.
All appropriate clinical, non-clinical security information should be given in Periodic Safety Update Report, global MAH status, product approval, removal or launch status must be given during the reporting interval and cumulative information must be submitted on severe, unlisted Adverse Drug Reaction. PSUR should concentrate on Adverse Drug Reaction (ADR) and whether modification needs to be made to the product safety data to optimize the product use.	When shifting PSUR to PBRER unless there is a change in the Data Lock Point (DLP) reporting frequency, the marketing authorisation holder can proceed without altering the new waiver application and if there are any changes to the DLP, marketing authorization holder must submit a new waiver request and a one-time PADER request. For a specific item, the PSUR reporting cycle is three years.	The PBRER must comprise new evidence related to a medical product that existed during the reporting interval by the marketing authorization holder, in the situation of collective information by • Specific original safety data that might influence the medical product's benefit risk profile. • Any fresh efficacy data acquired throughout the reporting period. • Evaluating the information obtained by the marketing authorization holder is same as earlier data of medical product risk-benefit profile. • For approved indication benefit-risk are evaluated, when new safety information has emerged • The PBRER should include suggested measures for optimizing the risk-benefit profile For a portion of the other documents such as DSUR, the PBRER content of several parts can be used as a modular approach basis such as PSUR requires one research for an active product, irrespective of its market approval for different formulations or dosage forms or separate indication.	DSUR's structure, design and duration emphasize the significance of a basic standard report in encouraging accuracy and effectiveness.

Table no 6: Types of aggregate reports

OBJECTIVES:

The safety information of the annual review is presented in a complete, throughout the period of reporting for drugs beneath the study and the data obtained at the time of reporting period should be in concurrence with the previous investigational drug safety. The potential risks which are identified should be summarized based on the current understanding and management. The clinical investigation and study result

should be updated .The safety issues which are revealed throughout the reporting period should be discussed in the DSUR. The DSUR must be summarized and offer the data to the controllers and sponsor that the risk outlines of investigational medicine is adequately observed. Marketing authorization holder shall submit PSUR as detailed in the list of EU reference date (EURD). For each active substance/combination contained in it, the EURD list provides the following information: PSUR submission frequency, DLP, Date for submission, Requirement for generic, well-established use of PSUR, herbal product, homeopathic and traditional medicine. MAH shall submit PSUR according to the following submission schedule. After the item has been authorized (not marketed) at an interval of six months, or after the item has been launched on the marketplace, regular PSUR must originally be continuous for the two years and then at an interval of 3 years.[14,15]

II. Conclusion:

The market for Pharmacovigilance is rapidly evolving to meet the increased demand of medicines, driven by the growing disease burden and aging geriatric population. There is a need to reassess and qualify the best Pharmacovigilance delivery model, which includes vetting the right PVO partners who are able to deliver efficient reports while minimizing risks of ADRs. The ability to compete and thrive in the changing drug safety landscape is directly correlated to their investment in harnessing and utilizing technology trends. After all, Pharmacovigilance is a field that at its core has a simple mission: to safeguard public health and promote the safe use of medicine. Thanks to advancements in technology, we are brought closer to a future with less and less deaths from preventable ADRs.[16]

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