PHARMACOVIGILANCE

Dr Apurv B Patel
1st year resident
Department of Pharmacology

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Overview

- Pharmacovigilance Methods
- WHO Program for Pharmacovigilance
- Pharmacovigilance Program of India (PvPI)

PHARMACOVIGILANCE METHODS

- ADRs monitoring of pharmaceutical drugs/vaccines can be done through:

1. Passive Surveillance
2. Active Surveillance

} Hypothesis generating methods

3. Comparative Observational Studies } Hypothesis testing methods

PASSIVE SURVEILLANCE

- Passive surveillance means no active measures are taken to look for adverse effects other than the encouragement of health care professionals & others to report safety concerns.

- Spontaneous or voluntary reporting is a type of passive surveillance.

- Other types of passive surveillance include: 1) Case series
  2) Case report
  3) Stimulated reporting

SPONTANEOUS REPORTING SYSTEM

- The Spontaneous Reporting System is a crucial method for monitoring the safety of medicines through the voluntary submission of Individual Case Safety Reports (ICSRs) by healthcare professionals, pharmaceutical manufacturers, and patients.

- Originating from the thalidomide tragedy in the 1960s, it aims to identify rare and unexpected adverse drug reactions (ADRs), contributing significantly to drug safety.

- Data from these reports are collected in VIGIBASE, managed by the Uppsala Monitoring Centre with WHO support.

- Reporting forms vary by country, with examples including India's "Suspected Adverse Drug Reaction Reporting Form," the UK's "Yellow Card," and the US's "MedWatch."

- In the US, there are two forms:

A. Form FDA **3500B** for voluntary

B. Form FDA **3500A** for mandatory reporting by the pharmaceutical industry, which must report serious unlabeled ADRs within 15 days, accounting for about 80% of ADR reports to the FDA.

- This system is essential for the early detection of drug risks and ensuring medication safety.

Advantages	Disadvantages
Covers the entire population and all medicines.	Significant underreporting results in incomplete data.
Low setup and maintenance costs.	Reporting bias and no denominator complicate risk assessment.
Allows continuous monitoring of medicines' lifecycle.	Ineffective at identifying delayed ADRs.
Detects new, rare, or serious ADRs missed in clinical trials.	Deaths and severe outcomes are underreported.

CASE REPORT & CASE SERIES

- Case reports provide detailed information on drug effects in one patient, sparking ideas for more research.
- Case series group together several case reports, suggesting possible links between a drug and side effects, but don't confirm these links.
- Both are useful for spotting and learning about specific drug-related issues like anaphylaxis and severe skin reactions.

STIMULATED REPORTING

- Stimulated reporting encourages health professionals to report side effects, especially when new medicines are launched or during specific times.

- It can be prompted by communications with healthcare professionals, public advisories, or meetings with medical representatives.

- This method collects more data on side effects early after a product is sold but has similar issues to spontaneous reporting, like selective and incomplete reporting.

ACTIVE PHARMACOVIGILANCE

- Active pharmacovigilance is a proactive approach to monitor drug safety by continuously tracking patient experiences during and after treatment.

- Unlike passive surveillance, which relies on voluntary reporting of adverse events, active pharmacovigilance uses methods like reviewing patient records, direct questioning, and regular lab tests to systematically collect detailed information on drug reactions.

- This allows for a more thorough understanding of adverse events, their frequency, and risk factors, leading to safer and more effective use of medicines.

- Methods of Active Surveillance:

1.Cohort Event Monitoring

2.Registries

3.Sentinel Sites

4.Drug event monitoring

COHORT EVENT MONITORING

- Cohort Event Monitoring (CEM), a form of active pharmacovigilance, is a prospective observational study designed to collect detailed safety data on new drugs during their **early post-marketing phase**.
- It involves enrolling patients into a cohort and actively following them to record adverse events using questionnaires sent to both prescribing physicians and patients at predetermined intervals.
- These questionnaires cover a range of information, including patient demographics, treatment details, and clinical events.
- CEM targets the first 5000 to 10,000 prescriptions of a new drug, aiming to estimate event incidence and identify potential risks.

- Although more labor-intensive and costly than passive reporting, CEM offers valuable insights into drug safety through direct patient feedback and continuous follow-up, making it an essential tool for evaluating drug safety in real-world settings.

Advantages	Disadvantages
Early detection of unsuspected ADRs	More labor intensive
Complete information regarding ADRs	More costly
Can calculate the incidence rate	Training required

REGISTRY

- Registries are organized systems that collect data on patients with certain commonalities, such as a specific disease, medication use, or pregnancy.
- Disease registries(registries for severe cutaneous reactions) focus on tracking the progression of specific conditions.
- Drug registries(registry of rheumatoid arthritis patients exposed to biological therapies) examine how healthcare products are used.
- Pregnancy exposure registries study the impacts of exposures during pregnancy on children.

SENTINEL SITES

- Sentinel sites are specific locations chosen for in-depth health data collection to guide broader health policies and programs.
- They provide valuable insights into disease trends, drug safety, and treatment outcomes by focusing on detailed data gathering within a selected area or community.
- This approach enables efficient monitoring and evaluation of health initiatives, offering a cost-effective method to understand and improve public health outcomes.

- Sentinel sites are particularly useful in pharmacovigilance for tracking adverse drug reactions and usage patterns, thereby enhancing drug safety monitoring.

- In pharmacovigilance, the role of sentinel sites is crucial for:

1) Early detection of new or rare adverse drug reactions.
2) Monitoring the safety of medications in specific populations, such as children or pregnant women.
3) Evaluating the impact of regulatory actions taken in response to identified drug safety concerns.
4) Informing healthcare professionals and the public about potential risks associated with drug therapies.

COMPARATIVE OBSERVATIONAL STUDIES

- Traditional epidemiological methods are a key component in the evaluation of adverse events.

- Observational study designs are useful in validating signals from spontaneous reports or case series.

- Types of Designs:

1. Cross-sectional studies
2. Case-control studies
3. Cohort studies (Both Retrospective & Prospective)

CROSS-SECTIONAL STUDY

- Cross-sectional studies, also known as surveys, are a type of research that collects information from a group of people at one moment in time.
- They're useful for finding out how common a condition is or for looking at relationships between different factors at that specific time.
- However, they can't prove that one thing causes another because they look at everything all at once.
- These studies often use questionnaires or interviews to gather data and are good for seeing how things are at a particular point and observing changes over time when repeated.

CASE-CONTROL STUDY

- Case-control studies compare people with a specific disease or adverse drug reaction (ADR) to those without it, looking back in time to see if there were differences in their exposure to possible risk factors.
- They use odds ratios to estimate the risk difference between those exposed and not exposed to these factors.
- These studies are great for examining rare conditions because they can efficiently collect and compare past exposure data.

- They often use existing health databases or registries to find cases and suitable controls, ensuring the control group accurately reflects the general population's exposure.

- Case-control studies can also focus on particular groups, like the elderly or pregnant women, to learn about drug safety in these populations.

Calculating the Odds Ratio (OR)

	Disease (Case)	No Disease (Control)
Exposed	A	B
Unexposed	C	D

$$OR = \frac{\text{Odds that a case was exposed } (A/C)}{\text{Odds that a control was exposed } (B/D)} \quad \frac{AD}{BC}$$

Advantages:

- Ability to study multiple drug exposures
- Suitable for investigating uncommon diseases
- Ease, speed, and cost-effectiveness of data collection

Disadvantages:

- Difficulty in finding appropriately matched controls
- Prone to recall bias, with affected individuals remembering events differently from those not affected
- Retrospective data collection can result in missing information

COHORT STUDY

- Cohort studies focus on groups of people who share a common characteristic or exposure to a certain factor, such as a specific medication, and track them over time to see how this exposure affects their health.

- They can be either prospective, where the study starts in the present and follows participants into the future, or retrospective, where researchers look back at existing data to examine past exposures and outcomes.

- In these studies:
- The cohort (group) is often defined based on exposure to a specific drug or condition, such as NSAIDs.
- Participants are divided into exposed and unexposed groups to compare the occurrence of diseases or adverse events between them.
- Prospective cohort studies actively collect data going forward and can specifically gather information relevant to the study but may take a long time and be expensive.

- Retrospective cohort studies use existing data, which allows for immediate analysis but may suffer from issues like difficulty in tracing subjects or relying on less accurate past records.

- Both types aim to identify if there is a link between the exposure and outcomes, such as diseases or adverse drug reactions, by comparing incidence rates between exposed and unexposed groups.

- Selection of subjects from the same population and ensuring they are at risk for the outcome are key for minimizing biases and improving study accuracy.

Advantages	Disadvantages
Calculate incidence rates	Cost
Study multiple outcomes	Time-consuming
Accurate exposure data	Difficulty in gathering participants
Less selection bias	Potential for biased outcome data

WHO PROGRAMME FOR INTERNATIONAL DRUG MONITORING

- In 1963, during the 16th World Health Assembly, resolution 16.36 called for "a systematic collection of information on serious adverse drug reactions during the development and particularly after medicines have been made available for public use".

- This led to the formation of the WHO programme for international drug monitoring (PIDM) in 1968.

- WHO PIDM members submit reports of adverse reactions associated with medicinal products, known as individual case safety reports (ICSRs) to the WHO global database, **VigiBase**.

- VigiBase is managed and maintained by the WHO collaborating centre for international drug monitoring, known as Uppsala monitoring centre.

- In july 2023, there were over 35 million reports of adverse reactions in VigiBase. Data in VigiBase are recorded in a structured and comprehensive way to allow the detection of potential medicinal safety hazards.

- Initially, the headquarters of the World Health Organization served as the coordination hub for the programme.
- Subsequently, in 1978, this role was transitioned to the Uppsala Monitoring Centre.
- While the World Health Organization headquarters retained authority over policy-making decisions, the operational facets of the programme were transferred to the Uppsala Monitoring Centre.

- The programme consists of a three-part network:

1) WHO Uppsala monitoring centre
2) National centre of member country
3) WHO Headquarter, Geneva

THREE WHO COLLABORATING CENTERS

- ✓ Uppsala Monitoring Center, Sweden
- ✓ The centre in Rabat, Morocco - WHO Collaborating Centre for Strengthening Pharmacovigilance Practices.
- ✓ WHO Collaborating Centre for Pharmacovigilance in Public Health Programme and Regulatory Services: Pharmacovigilance Programme of India (PvPI) – Indian Pharmacopoeia Commission, Ghaziabad.

UPPSALA MONITORING CENTRE

- **Functions:**

- Collecting, assessing, and communicating information from member countries regarding the benefits, harm, effectiveness, and risks of drugs.
- Collaborating with member countries on the development and practice of pharmacovigilance.
- Alerting national regulatory authorities (NRAs) of member countries about potential drug safety problems through the WHO signal process.

- The Uppsala Monitoring Centre (UMC) develops and provides several software tools to support National Centers in the International Drug Monitoring Programme, including:

- **VigiBase :** The WHO's global database, archives millions of adverse drug effect reports since 1968, making it the largest of its kind.

- Continuously updated, it uses WHO's Drug Dictionary and WHO-ART(Adverse Reaction Terminology), along with other classifications like MedDRA(Medical Dictionary for Regulatory Activities) and WHO ICD(International Classification of Diseases), for detailed data management.

- **VIGILYZE** is a tool that lets members of the WHO Programme for International Drug Monitoring (PIDM) search and analyze over 35 million individual case safety reports (ICSRs) in VigiBase.

- **VIGIACCESS** offers the public a way to access VigiBase, allowing people to search for and retrieve statistical data about safety concerns reported to the WHO PIDM.

- **VIGIFLOW** is an online system designed for national centers in the WHO PIDM to manage ICSRs.

- **VIGIFLOW_e-Reporting_** is an additional feature of VIGIFLOW that enables national centers to receive ICSRs directly from patients and healthcare professionals via the web.

THE CENTRE IN RABAT, MOROCCO

- The WHO Collaborating Centre for Strengthening Pharmacovigilance Practices, established as a Collaborating Centre in 2011, focuses on enhancing patient safety and pharmacovigilance in Africa.

- It conducts regional and national training, supports patient safety initiatives, and covers various topics including pharmacovigilance for herbal medicines, vaccines, and medication errors.

- The Centre is also involved in integrating patient safety reporting systems and improving pharmacovigilance in public health programs.

WHO COLLABORATING CENTRE FOR PHARMACOVIGILANCE IN PUBLIC HEALTH PROGRAMMES AND REGULATORY SERVICES:

- The Pharmacovigilance Programme of India (PvPI), located at the Indian Pharmacopoeia Commission in Ghaziabad, was recognized as a WHO Collaborating Centre in 2017.

- Its main goal is to protect the health of India's 1.27 billion people by monitoring and reporting adverse drug reactions (ADRs) across the country.

- PvPI works closely with the WHO's global drug monitoring program and contributes to the international database of ADRs.

- It supports WHO by helping to develop tools and guidelines to improve pharmacovigilance practices, especially in low and middle-income countries in Asia and elsewhere.

MAJOR FUNCTION OF WHO PROGRAM FOR INTERNATIONAL DRUG MONITORING INCLUDE

- Analyzing new adverse drug reactions using national reports and the WHO database.
- Facilitating information exchange and discussions via VIGIMED, a drug safety IT tool.
- Offering training and consultancy in Pharmacovigilance.
- Conducting annual meetings for global drug monitoring and safety issues discussion.

PHARMACOVIGILANCE PROGRAMME OF INDIA

- **1986** :India started its ADR monitoring programme with 12 regional centers.

- **1998** :India joined WHO-ADR reporting program based in Uppsala, Sweden with 3 WHO special centers.

- 3 centers: AIIMS (New Delhi)
  KEM (King Edward Memorial hospital)
  JLN hospital, AMU (Aligarh Muslim University)

- **2004-2008**: The National Pharmacovigilance Program (NPP) was launched by India's Central Health Minister in New Delhi, under the guidance of the Ministry of Health and Family Welfare and coordinated by the Central Drugs Standard Control Organization (CDSCO).

- The program was initiated with two zonal centers:

1) The South-West Zonal Centre at KEM, Mumbai

2) The North-East Zonal Centre at AIIMS, New Delhi.

- In addition to the two zonal centers, the program also included five regional centers:

1) AIIMS New Delhi
2) PGIMER in Chandigarh
3) Sanjay Gandhi Postgraduate Institute of Medical Sciences in Lucknow
4) King Edward Memorial Hospital in Mumbai
5) Christian Medical College in Vellore.

- **July 2010** :The Pharmacovigilance Programme of India (PvPI) was initiated with AIIMS, New Delhi serving as the National Coordination Centre (NCC) for monitoring Adverse Drug Reactions (ADRs) in the country.

- Dr. Surinder Singh, the former Drug Controller General of India (DCGI), was responsible for relaunching the National Pharmacovigilance Programme in India on 14th July 2010 with its own budgetary support.

- On **15th April 2011**, the **NCC was shifted from AIIMS**, New Delhi, to the **Indian Pharmacopoeia Commission (IPC)** in Ghaziabad**.**

Indian Pharmacopoeia Commission:

- The Indian Pharmacopoeia Commission (IPC) is an independent body under India's Ministry of Health and Family Welfare, serving as the National Coordination Centre for the country's pharmacovigilance program.
- Its primary responsibility is to monitor and assess adverse drug reactions within the Indian population.
- The IPC also aims to create and manage a pharmacovigilance database to ensure patient safety regarding medication use in India, facilitating regulatory actions tailored to the needs of the Indian population.

❑ The Minimum Requirements for a functional Pharmacovigilance System

1.A National Pharmacovigilance Centre should have dedicated staff (at least one full-time), reliable funding, clear mandates, well-defined structures and roles, and should collaborate with the WHO Programme for International Drug Monitoring.

2.The existence of a National spontaneous reporting system with a national individual case safety report (ICSR) form i.e. ADR reporting form.

3.A national database or system for gathering and managing ADR reports. (Vigiflow)

4.A national committee for ADR or pharmacovigilance that offers expert advice on determining cause, assessing and managing risks, investigating cases, and handling crisis situations, including communication during crises.

5.Clear communication strategy for routine communication and crises communication.

MISSION

- Safeguard the health of the Indian population by ensuring that the benefits of use of medicine outweigh the risks associated with its use.

VISION

- To improve patient safety and welfare in Indian population by monitoring drug safety and thereby reducing the risk associated with use of medicines.

Objectives of Pharmacovigilance programme of India:

- To create a nationwide system for reporting patient safety incidents.
- To identify and analyze new signals from reported cases.
- To evaluate the benefit-risk ratio of marketed medications.
- To produce evidence-based information on the safety of medicines.
- To assist regulatory agencies in the decision-making process regarding the use of medications.

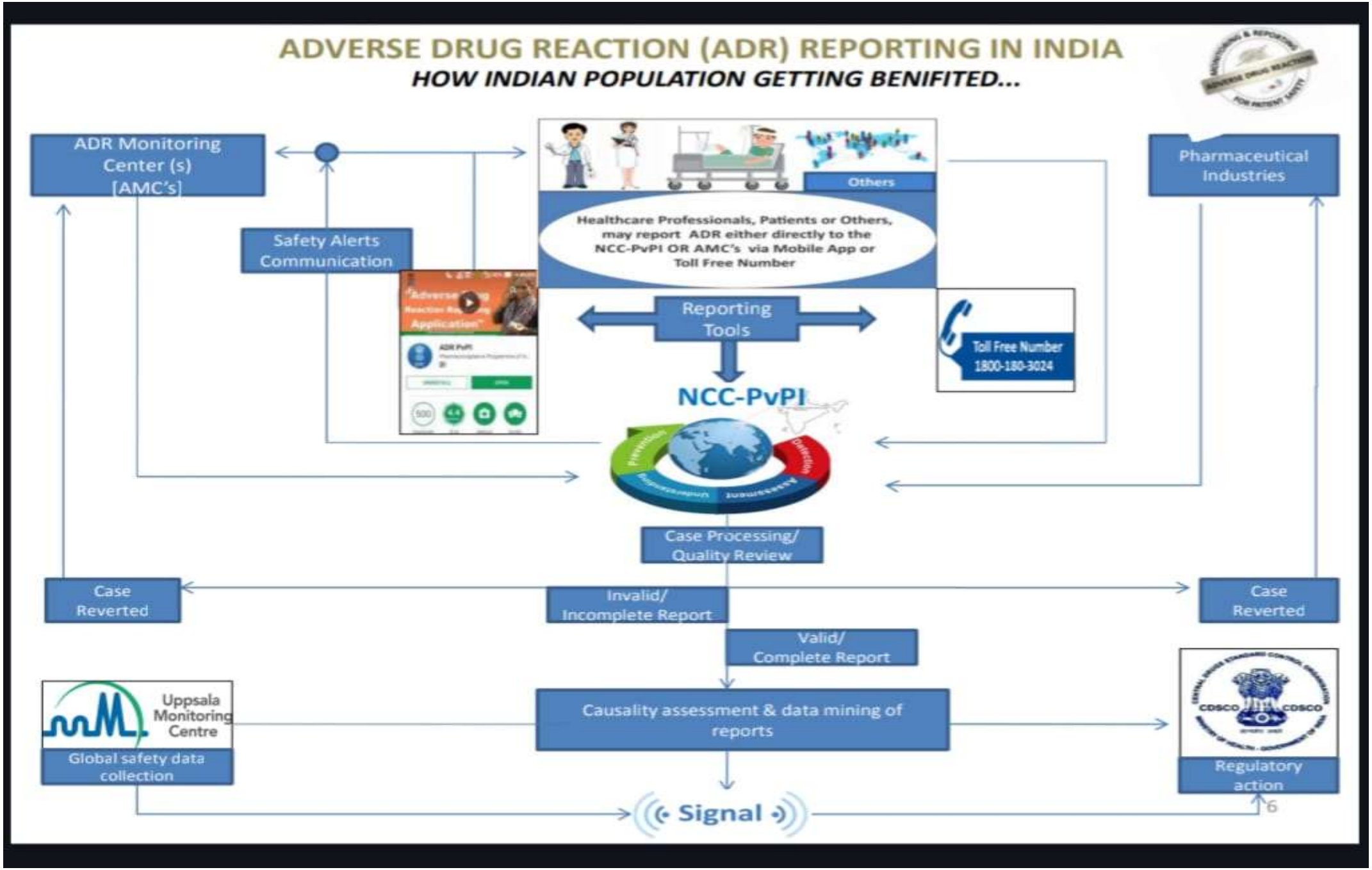
- To encourage the rational use of medicine.
- To communicate safety information about the use of medicines to various stakeholders to minimize risks.
- To collaborate with national centers for the exchange of information and data management.
- To provide training & consultancy support to other Pharmacovigilance centers across the globe.

Short term Goals

- To develop & implement pharmacovigilance system in India.
- To enroll initially all MCI approved medical colleges in the program. covering North, South, East and West of India.
- To encourage HCP's in reporting of ADRs to drugs, vaccines, medical devices and biological products.
- Collection of case reports & data.

Long term Goals

- To expand the PvPI to all hospitals (govt. & private), public heath programs located across India.
- To develop & implement e- reporting system.
- To develop reporting culture amongst HCPs.(Healthcare professionals)
- To make ADR reporting mandatory for HCPS.


ADVERSE DRUG REACTION (ADR) REPORTING IN INDIA
HOW INDIAN POPULATION GETTING BENIFITED...
ADR Monitoring Center (s) [AMC's]
Safety Alerts Communication
Others
Healthcare Professionals, Patients or Others, may report ADR either directly to the NCC-PvPI OR AMC's via Mobile App or Toll Free Number
Reporting Tools
Toll Free Number 1800-180-3024
Pharmaceutical Industries
NCC-PvPI
Case Processing/ Quality Review
Case Reverted
Invalid/ Incomplete Report
Valid/ Complete Report
Case Reverted
Uppsala Monitoring Centre
Global safety data collection
Causality assessment & data mining of reports
CDSCO
Regulatory action
Signal

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PHARMACOVIGILANCE COMMITTEE OF PIMSR

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15	Mr. Deepak Patel	Pharmacy IN-charge	Member

REFERENCES

1.Gupta SK, india. Textbook of pharmacovigilance. New delhi: jaypee brothers medical publishers; 2011.1-38

2.Pvpi [internet]. Cdsco.Gov.In. Available from: https://cdsco.Gov.In/opencms/opencms/en/pvpi/

3.Pharmacovigilance Programme of India [Internet]. Ipc.gov.in. 2019 [cited 2023 Dec 29]. Available from: https://ipc.gov.in/PvPI/pv_home.html

4.Programme for International Drug Monitoring [Internet]. www.who.int. Available from: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance/networks/pidm


Thank You!