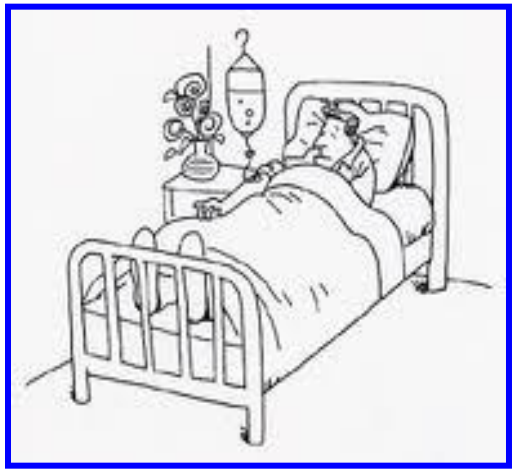
Pharmacovigilance Programme of India (PvPI):
Progress and Challenges ahead

Prof. YK Gupta
National Scientific Coordinator, PvPI

Facts about safety of Medicines

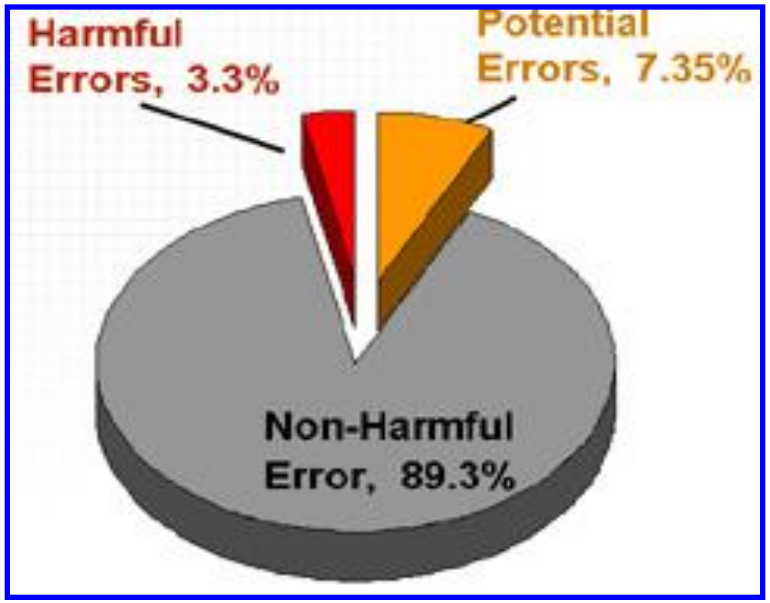
- The incidence of drug-related admissions range from 0.2 to 22% (WHO Data)
- Nearly 10–20% of acute geriatric hospital admissions are related to ADRs



Indian data need to be generated

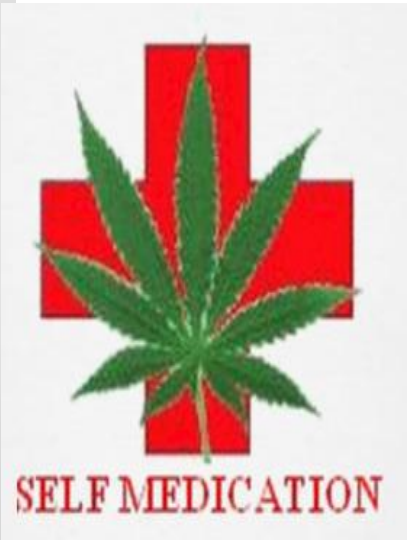
WHO Data

- Nearly 7% of medication errors potentially harmful but preventable ADRs



Indian data need to be generated

- **Worldwide** more than 50% of all medicines are prescribed, dispensed or sold inappropriately



- 50% of patients fail to take them correctly

Increased ADR's

- ↑ Prolongation of Hospital Stay (median 5 days)
- Decreased compliance
- Drug Resistance and Cost Implications (USD 150 per patient)

CAN HE AFFORD AN ADR ???

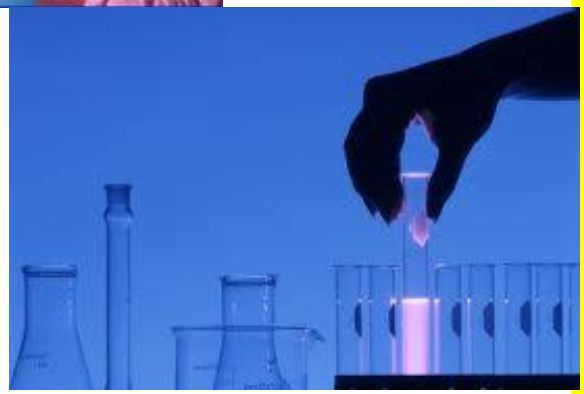
Patel et al. BMC Clin Pharmacol. 2007 Jul 28;7:8

Scope of Pharmacovigilance

New Drugs and Spontaneous Reporting

- **Medication errors and irrational use of medicines**
- **Herbal, traditional and complimentary medicines**
- **Substandard medicines and counterfeit medicines**
- **Blood products, biologicals, medical devices and vaccines**

Need for Translational Pharmacovigilance



Clinical Research

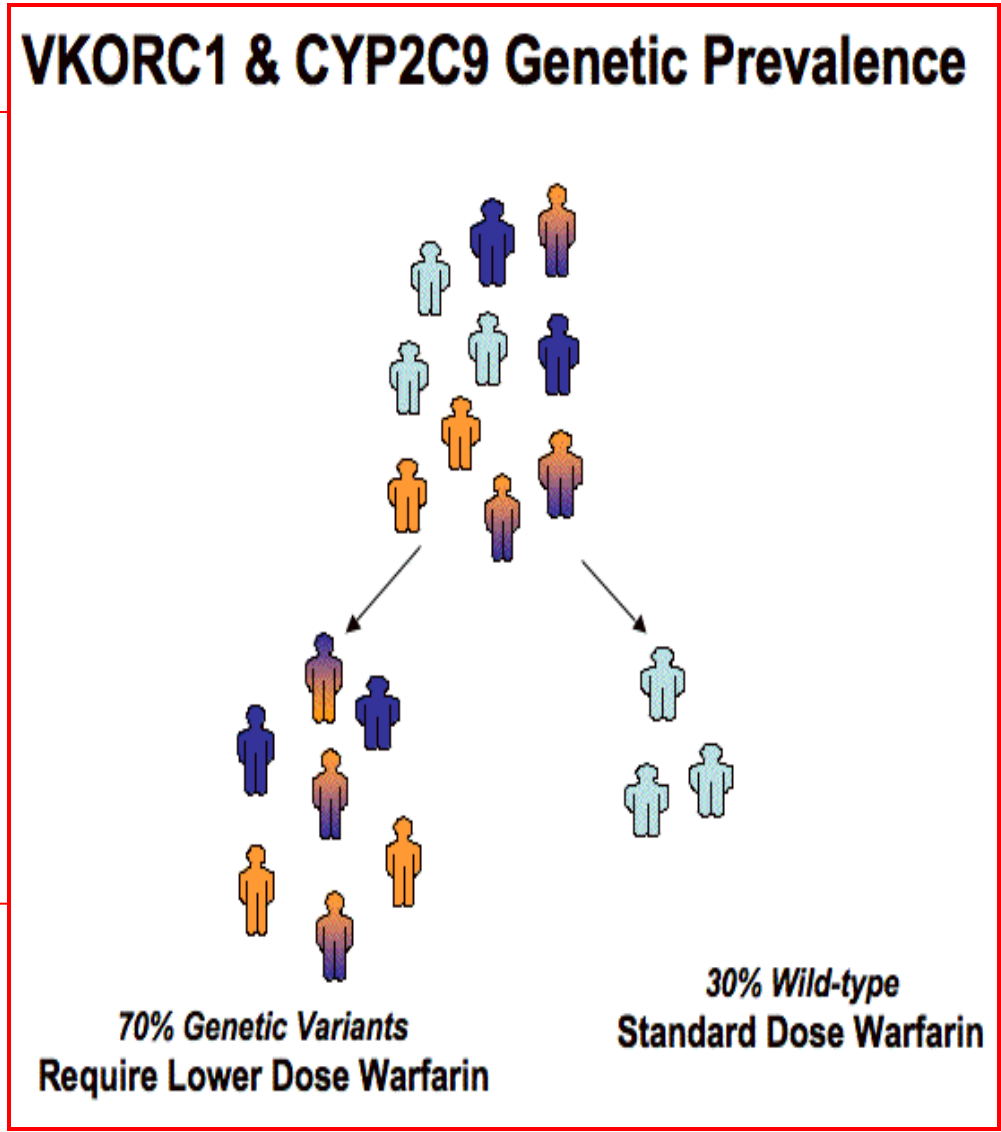
Practice

Transition from bench to bedside

Genomics and Pharmacovigilance

Warfarin - the most widely prescribed oral anticoagulant

Label advice *(2007)*: Altered metabolism of warfarin in patients with particular variants in the cytochrome P450 2C9 (*CYP2C9)* or vitamin K epoxide reductase complex subunit 1 (*VKORC1) genes* ***requires dose adjustment.***

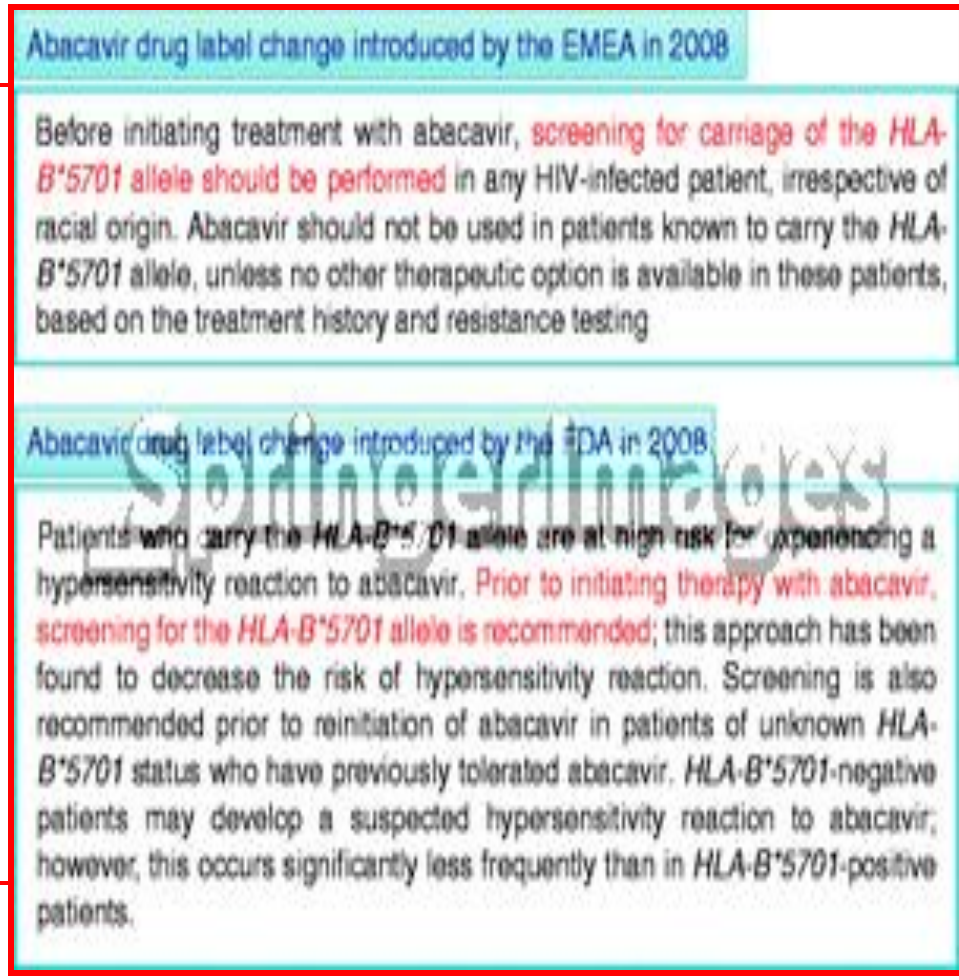


Transition from bench to bedside

Genomics and Pharmacovigilance

Abacavir – antiretroviral agent

Patients who carry the **HLA-B*5701 allele** are at high risk for experiencing a **hypersensitivity reaction** to abacavir. Prior to initiating therapy with abacavir, screening for the HLA-B*5701 allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction.



Abacavir drug label change introduced by the EMEA in 2008

Before initiating treatment with abacavir, screening for carriage of the *HLA-B*5701* allele should be performed in any HIV-infected patient, irrespective of racial origin. Abacavir should not be used in patients known to carry the *HLA-B*5701* allele, unless no other therapeutic option is available in these patients, based on the treatment history and resistance testing

Abacavir drug label change introduced by the FDA in 2008

Patients who carry the *HLA-B*5701* allele are at high risk for experiencing a hypersensitivity reaction to abacavir. Prior to initiating therapy with abacavir, screening for the *HLA-B*5701* allele is recommended; this approach has been found to decrease the risk of hypersensitivity reaction. Screening is also recommended prior to reinitiation of abacavir in patients of unknown *HLA-B*5701* status who have previously tolerated abacavir. *HLA-B*5701*-negative patients may develop a suspected hypersensitivity reaction to abacavir; however, this occurs significantly less frequently than in *HLA-B*5701*-positive patients.

Transition from bench to bedside

Genomics and Pharmacovigilance

Carbamazepine – antiepileptic

Testing for the **HLA-b*1502 allele in Asians** is recommended to identify individuals who are at increased **risk for Stevens–Johnson syndrome or toxic epidermal necrolysis** after taking **carbamazepine**

PV Challenges in India

Spontaneous ADR Reporting

- Long term safety data can only be captured through pharmacovigilance
  - SAEs
  - SUSARs
- Safety data obtained through clinical trials are from “Controlled situation”

Process in Pharmacovigilance

- **C**ollect and record of AEs / ADRs
- **C**ausality assessment and analysis of ADRs
- **C**ollate and code in database
- **C**ompute risk-benefit and suggest regulatory action
- **C**ommunicate for safe use of drugs among stakeholders

Process in Pharmacovigilance

- Collect and record of AEs / ADRs
- Causality assessment and analysis of ADRs
- Collate and code in database
- Compute risk-benefit and suggest regulatory action
- Communicate for safe use of drugs among stakeholders

Adverse Event reporting Form

ADVICE ABOUT REPORTING

- **Report adverse experiences with medications**
- **Report serious adverse reactions. A reaction is serious when the patient outcome is:**
  - death
  - life-threatening (real risk of dying)
  - hospitalization (initial or prolonged)
  - disability (significant, persistent or permanent
  - congenital anomaly
  - required intervention to prevent permanent impairment or damage
- **Report even if:**
  - You're not certain the product caused adverse reaction
  - you don't have all the details, however, point nos. **1, 5, 7, 8, 11, 15, 16 & 18** (see reverse) are essentially required.
- **Who can report:**
  - Any health care professional (Doctors including Dentists, Nurses and Pharmacists)
- **Where to report:**
  - Please return the completed form to the nearest ***Adverse drug reaction Monitoring Centre (AMC)*** or to ***National Coordinating Centre***
  - A list of nationwide AMCs is available at: http://cdsco.nic.in/pharmacovigilance.htm
- **What happens to the submitted information:**
  - Information provided in this form is handled in strict confidence. The causality assessment is carried out at Adverse Drug Reaction Monitoring Centres (AMCs) by using WHO-UMC scale. The analyzed forms are forwarded to the National Coordinating Centre through the ADR database. Finally the data is analyzed and forwarded to the Global Pharmacovigilance Database managed by WHO Uppsala Monitoring Center in Sweden.
  - The reports are periodically reviewed by the National Coordinating Centre (PvPI). The information generated on the basis of these reports helps in continuous assessment of the benefit-risk ratio of medicines.
  - The information is submitted to the Steering Committee of PvPI constituted by the Ministry of Health and Family Welfare. The Committee is entrusted with the responsibility to review the data and suggest any interventions that may be required.

Suspected Adverse Drug Reaction Reporting Form

For VOLUNTARY reporting
of suspected adverse drug reactions by
health care professionals

Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhawan, ITO, Kotla Road, New Delhi -110002
www.cdsco.nic.in

Pharmacovigilance Programme of India for *Assuring Drug Safety*

Pharmacovigilance Programme of India (PvPI)
National Coordinating Centre,
Department of Pharmacology,
All India Institute of Medical Sciences
Ansari Nagar, New Delhi – 110029
Phone no: 011-26593282, 26588422
Fax no: 011- 11-26588663, 26588641
Email: pvpi.ncc@gmail.com

Confidentiality: The patient's identity is held in strict confidence and protected to the fullest extent. Programme staff is not expected to and will not disclose the reporter's identity in response to a request from the public. Submission of a report does not constitute an admission that medical personnel or manufacturer or the product caused or contributed to the reaction.

SUSPECTED ADVERSE DRUG REACTION REPORTING FORM

For VOLUNTARY reporting of Adverse Drug Reactions by healthcare professionals

CDSCO
Central Drugs Standard Control Organization
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
FDA Bhawan, ITO, Kotla Road, New Delhi -110002
www.cdsco.nic.in

AMC/ NCC Use only
AMC Report no.
Worldwide Unique no.

A. Patient information

1. Patient initials
2. Age at time of Event or date of birth
3. Sex ☐ M ☐ F
4. Weight: _____Kgs

B. Suspected Adverse Reaction

5. Date of reaction started (dd/mm/yy):
6. Date of recovery (dd/mm/yy):
7. Describe reaction or problem

12. Relevant tests/ laboratory data with dates

13. Other relevant history, including pre-existing medical conditions (e.g., allergies, race, pregnancy, smoking, alcohol use, hepatic/ renal dysfunction, etc.)

14. Seriousness of the reaction
☐ Death (dd/mm/yy)_____
☐ Life threatening
☐ Hospitalization-initial or prolonged
☐ Disability
☐ Congenital anomaly
☐ Required intervention to prevent permanent impairment/ damage
☐ Other (specify)_____

15. Outcomes
☐ Fatal ☐ Recovering ☐ Unknown
☐ Continuing ☐ Recovered ☐ Other (specify)_____

C. Suspected medication(s)

Sl. No.	6. Name (brand and / or generic name)	Manufac-turer (if known)	Batch No. / Lot No. (if known)	Exp. Date (if known)	Dose used	Route used	Frequency	Therapy dates (if unknown, give duration)		Reason for Use or prescribed for
								Date started	Date stopped	
i										
ii										
iii										
iv										

Sl. No. As per C	9. Reaction abated after drug stopped or dose reduced					10. Reaction reappeared after reintroduction				
	Yes	No	Unknown	NA	Reduced dose	Yes	No	Unknown	NA	If reintroduced, dose
i										
ii										
iii										
iv										

11. Concomitant medical products including self medication and herbal remedies with therapy dates (exclude those used to treat reaction)

D. Reporter (see confidentiality section in first page)

16. Name and Professional Address: _____

Pin code: _____ E-mail: _____
Tel. No. (with STD Code): _____
Occupation: _____ Signature:

17. Causality Assessment:
18. Date of this report (dd/mm/yy)

AE/ ADR reports: Sources

- **Spontaneous Reporting Systems**

  - From Health care Professionals (voluntary)-high incidence of under reporting

- Published scientific literature: Pubmed, Scopus etc.
- Periodic Safety Update Report (PSUR)

Other methods for collecting AEs/ ADRs

ACTIVE SURVEILLANCE

- **Site surveillance** (hospitals, pharmacies, nursing homes etc.)
- **Focused ADR monitoring of drugs**
- **Prescription event monitoring**
- **Disease registries from Public health Programme**

COMPARATIVE OBSERVATIONAL STUDIES

- **Cross sectional survey**
- **Case control study**
- **Cohort studies**
- **Large safety trial**
- **Drug utilization study**

Process in Pharmacovigilance

- Collect and record of AEs / ADRs
- Causality assessment and analysis of ADRs
- Collate and code in database
- Compute risk-benefit and suggest regulatory action
- Communicate for safe use of drugs among stakeholders

Causality Assessment (CA) and Analysis of AEs/ADRs

Assessment and Analysis

- Quality check for completeness of the reported case
- Validity of the case
- Perform case follow-up (if necessary)
- Causality assessment

Causality Assessment (CA) and Analysis of ADRs

Quality and Validity

- Check for the Mandatory fields
- Valid report should have
  - Patient information
  - Date of Reaction
  - Adverse event
  - Suspected medication
  - Reporter (Source)

Causality Assessment (CA) and Analysis of ADRs

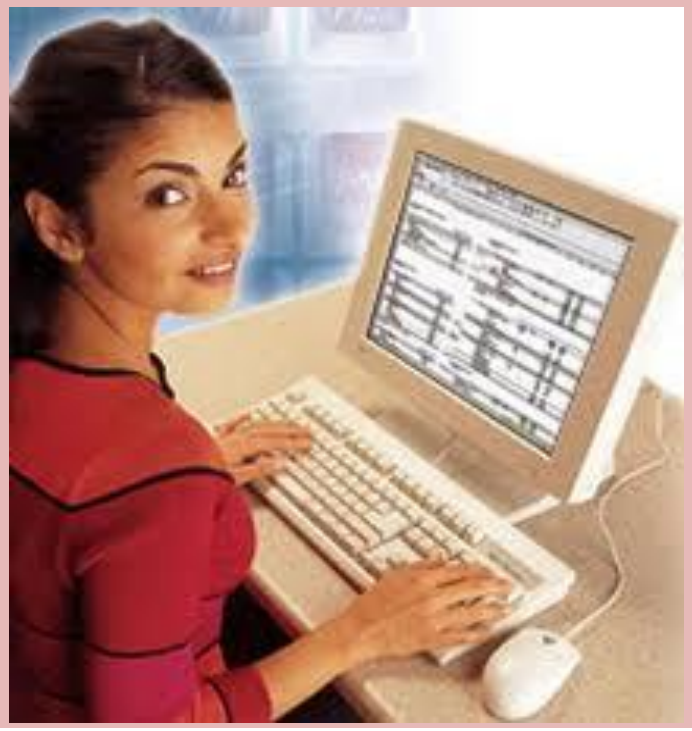
- **CA Scale**
  - Bayesian system
  - European ABO system
  - Jones scale
  - Karch & Lasagna scale
  - Kramer's scale
  - **Naranjo's scale**
  - Spanish quantitative imputation scale
  - **WHO-UMC probability scale**

Process in Pharmacovigilance

- Collect and record of AEs / ADRs
- Causality assessment and analysis of ADRs
- Collate and code in database
- Compute risk-benefit and suggest for regulatory action
- Communicate for safe use of drugs among stakeholders

Collate and Code in database

- ADR reports entry in Database

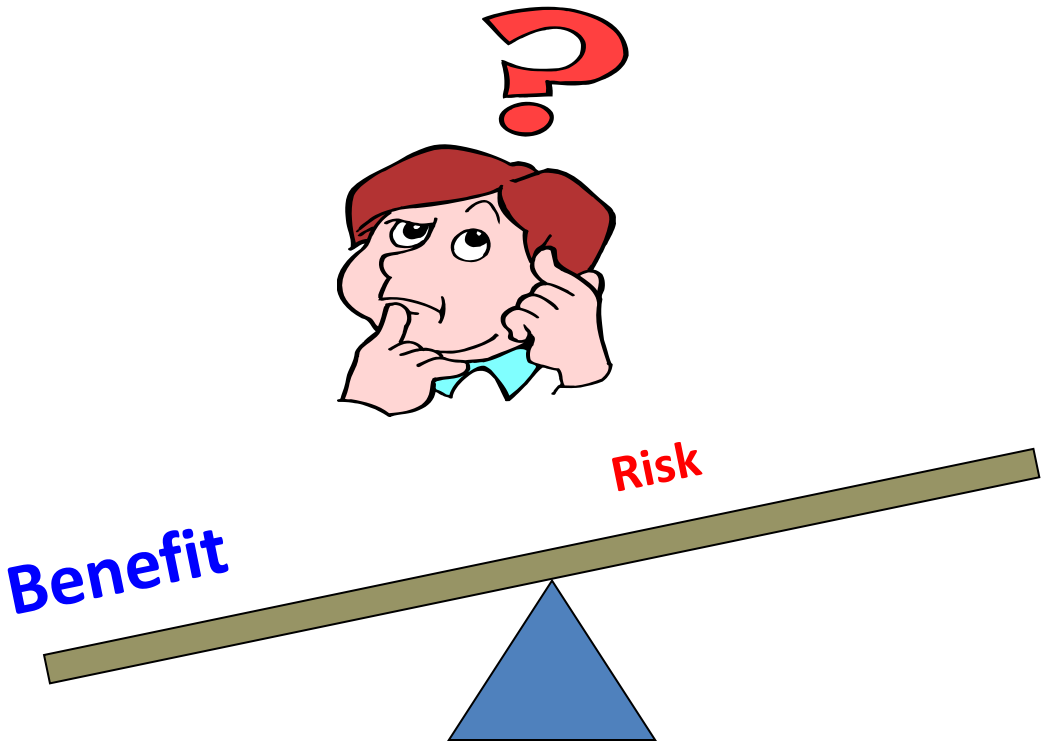


- Coding of events and drugs
  - Events
    - WHO-ART
    - MedDRA
  - Drugs
    - WHO-Drug dictionary

Process in Pharmacovigilance

- Collect and record of AEs / ADRs
- Causality assessment and analysis of ADRs
- Collate and code in database
- Compute risk-benefit and suggest regulatory action
- Communicate for safe use of drugs among stakeholders

Compute risk-benefit ratio



One man's meat is another man's poison !!!

Compute risk-benefit ratio

Signal

Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Drug Safety 1994

Suggest Regulatory Action

- **Suggest warnings and alerts for regulatory agency**

Widening Scope in Pharmacovigilance

ADR reports of new drugs

- Medication errors and irrational use of medicines
- Herbal, traditional and complimentary medicines
- Substandard medicines and counterfeit medicines
- Blood products, biologicals, medical devices and vaccines

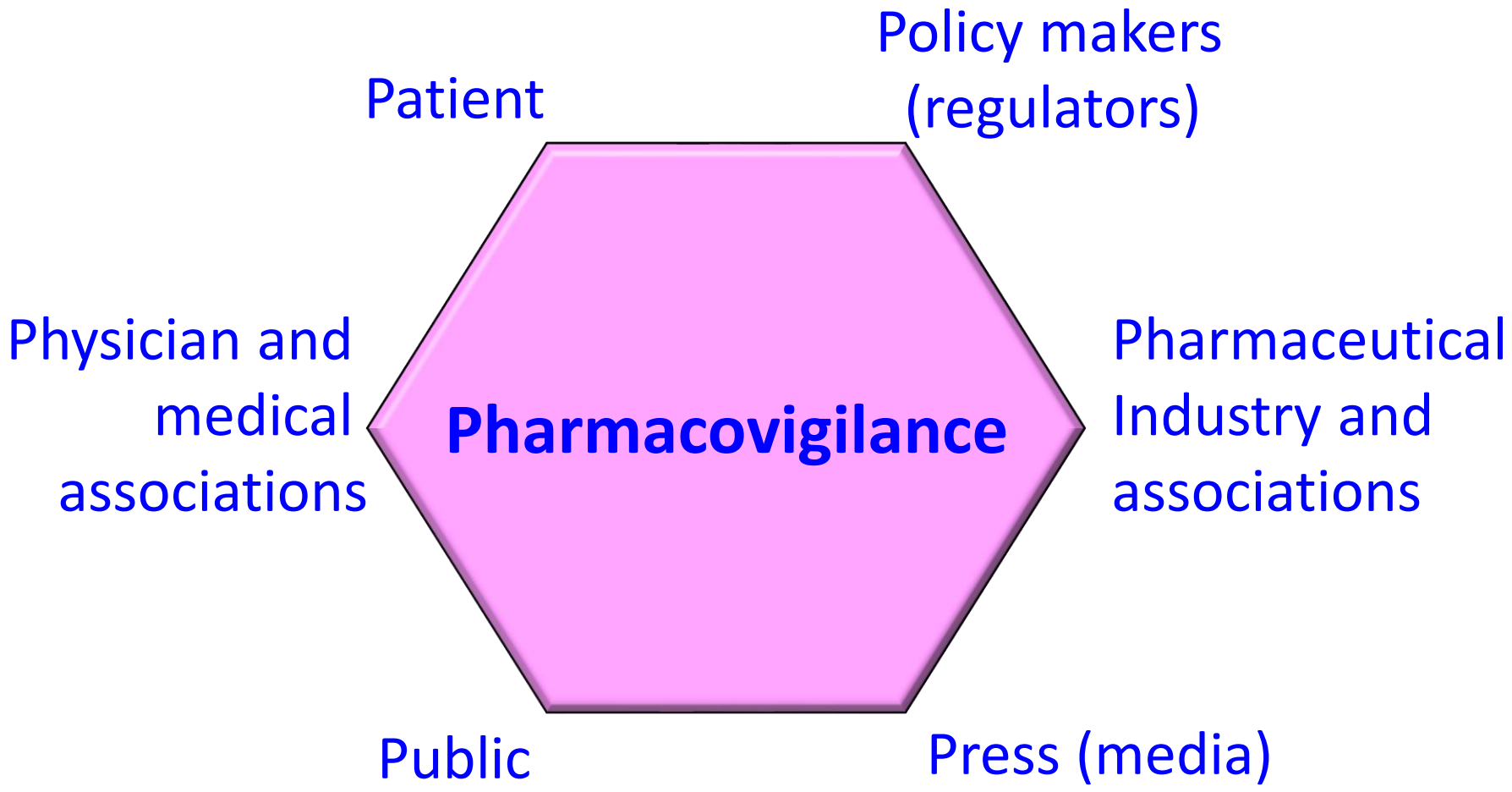
Drugs recently banned in India

- Rosiglitazone
- Sibutramine
- Rimonabant
- Nimesulide (Under 12 years)
- Cisapride
- Phenylpropanolamine
- Gatifloxacin and
- Tegaserod

Process in Pharmacovigilance

- Collect and record of AEs / ADRs
- Causality assessment and analysis of ADRs
- Collate and code in database
- Compute risk-benefit and suggest regulatory action
- Communicate for safe use of drugs among stakeholders

Communication among Stakeholders



Lag Period between Signal Detection & Regulatory Action

Quality control of PV data

- Quality of Individual Case Safety Reports
- Incomplete/ missing information
- Inconsistencies in reporting
  - Coding of reaction terminologies
    - WHO-ART/ MedDRA
    - **India???**

      use of local terms like:

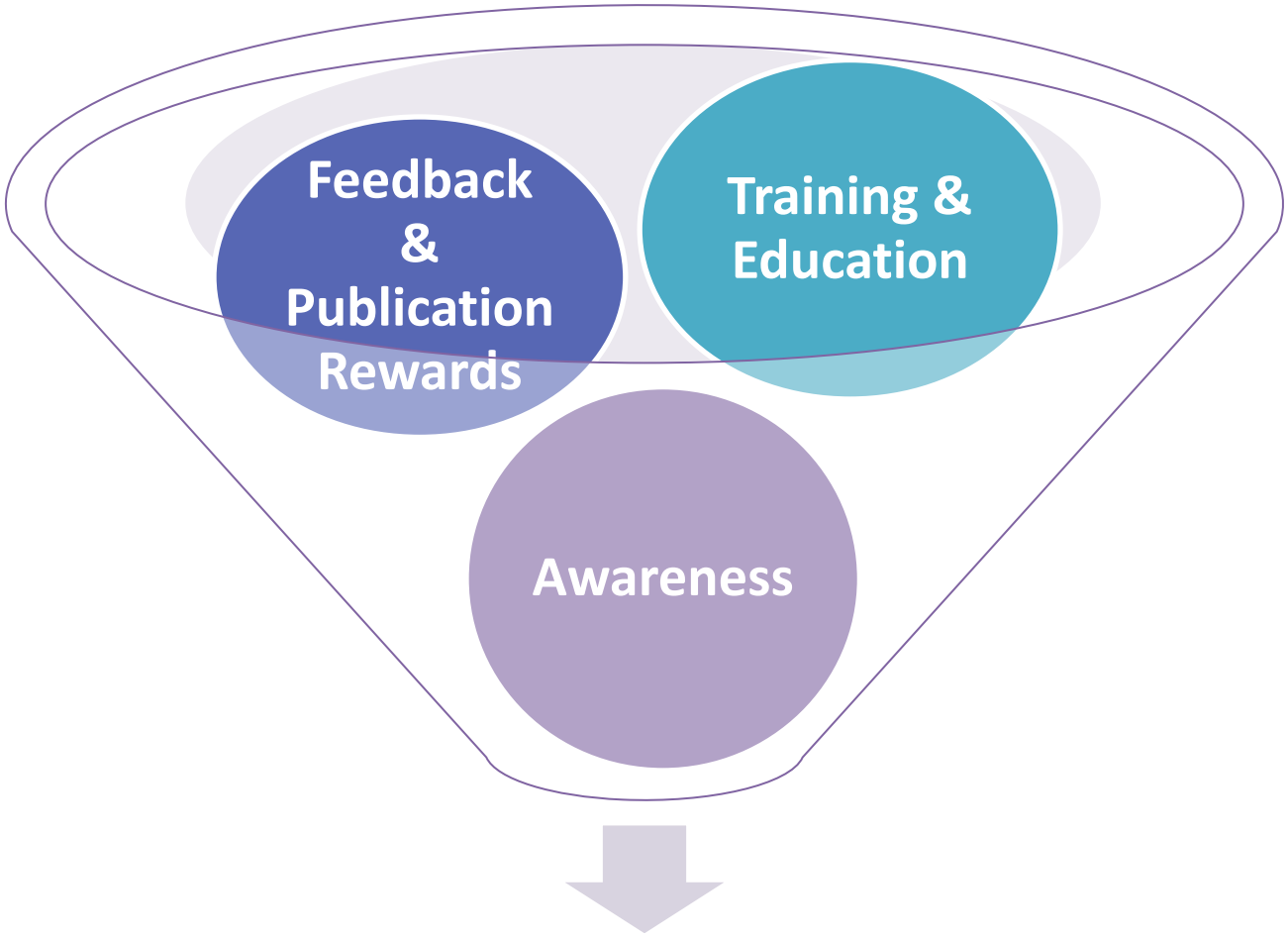
      “mata” for ?chicken pox ?measles

      “mirgi” for ?epilepsy ?hysteria
- Periodic Quality Assessment

Reasons for underreporting

- Considered as additional burden
  - Little obvious or immediate return
  - Time consuming
- To avoid scrutiny of professional competence
- Insufficient awareness/ training

Improving AE Reporting

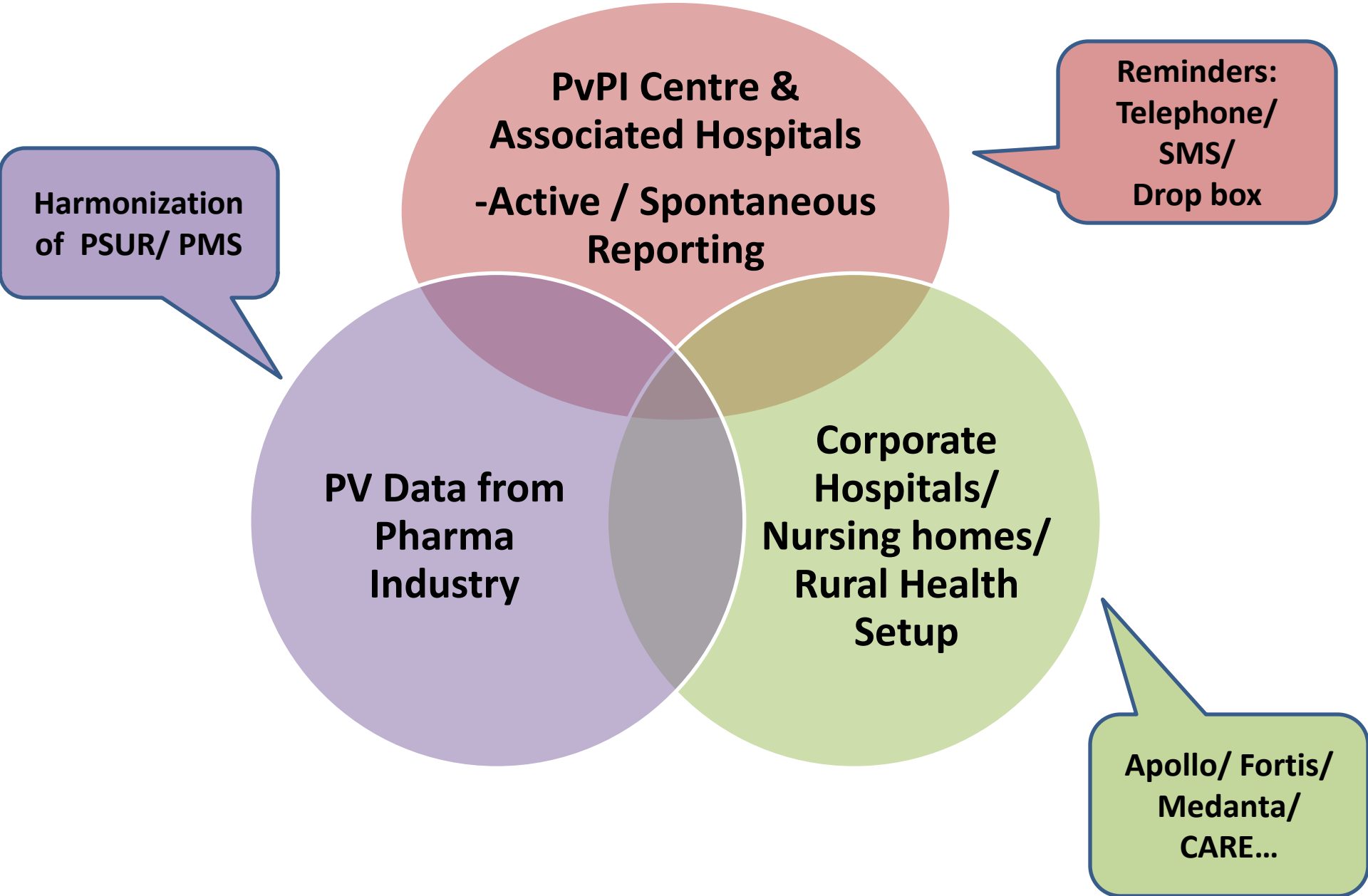


Good Reporting Practice

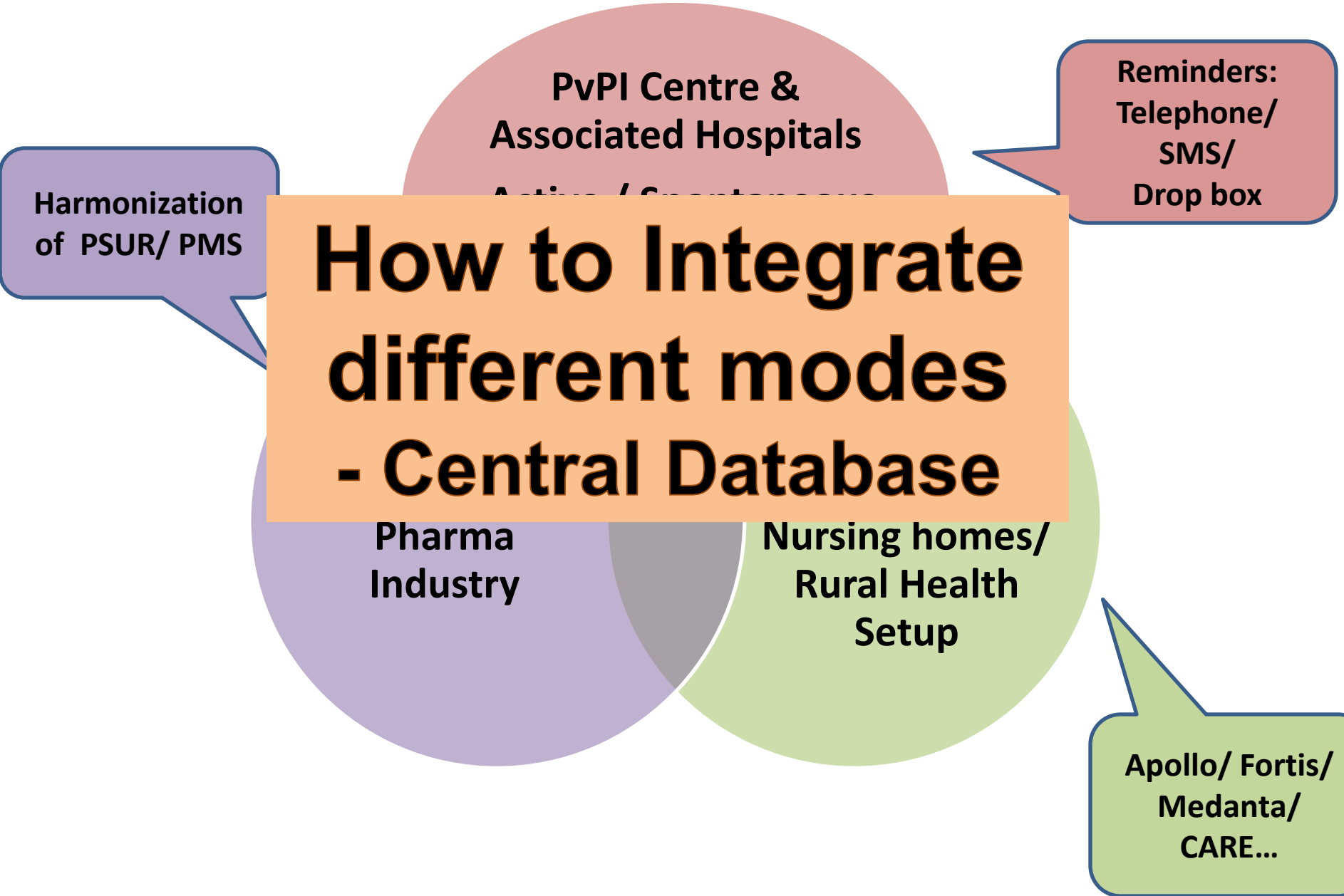
Interaction with Physicians & Paramedics

- Developing one-to-one rapport
- Two way communication

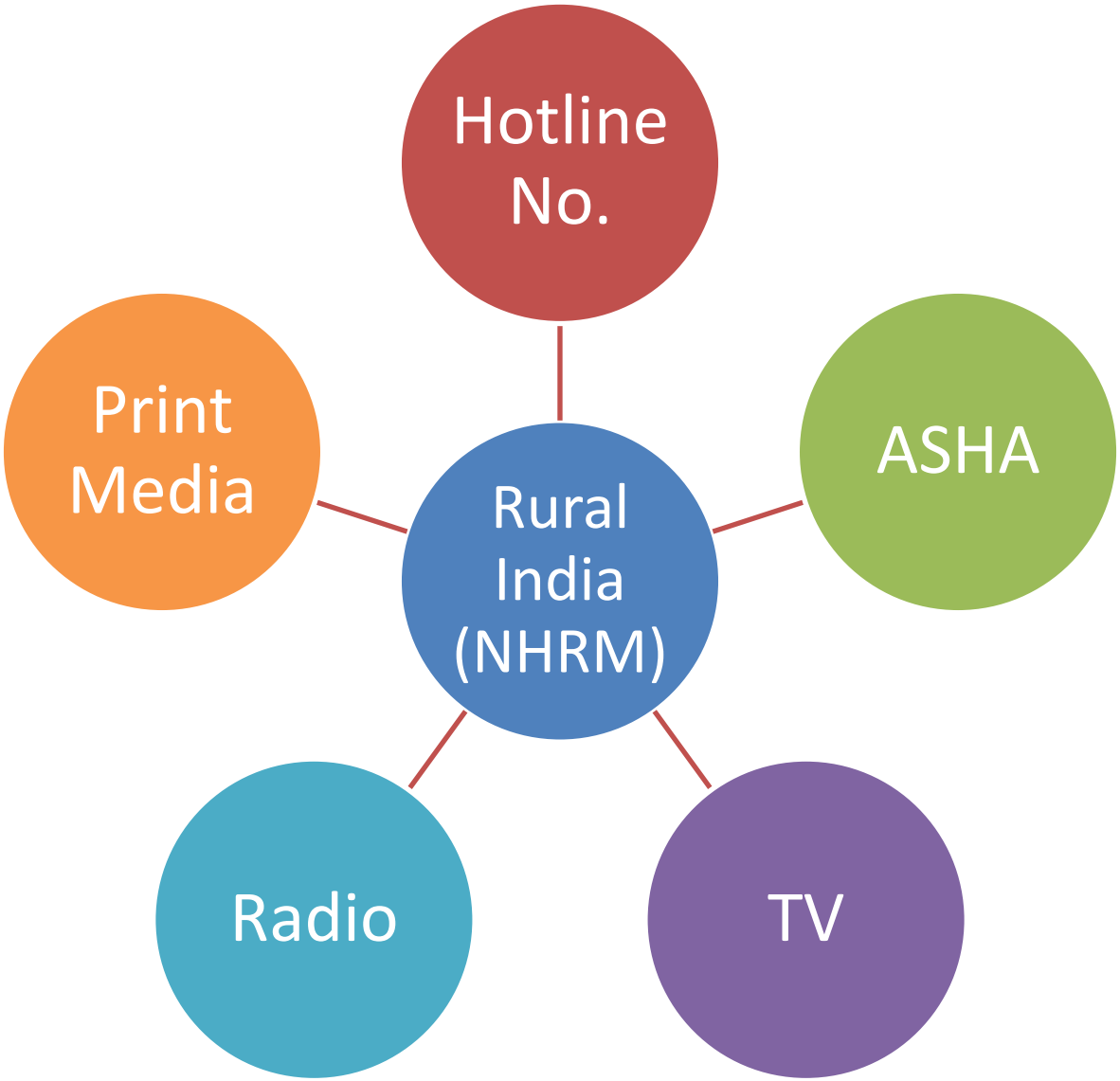
Hybrid AE Reporting Model



Hybrid AE Reporting Model



Reaching rural India for PV



Education in PV

- Catch them young philosophy
  - UG Curriculum (MBBS, Pharmacy, Nursing)
- Continuing education for postgraduates
- CMEs for practicing healthcare professionals
- Role of M.C.I, P.C.I., I.N.C.

PV Education…

- **The Good**
  - Help sustain reporting culture
- **The Bad**
  - Mushrooming of PV course providers
- **The Ugly**
  - Training by untrained professional
  - Lack of standard training

Media management & PV in India

- Publicity driven reporting
  - Over reporting
  - Misreporting
- Due/ Undue public scare

Where do we stand?

Challenges for India

- Safety data from developed countries may not be directly applicable
  - Difference in genotype and phenotype of pts
  - Social and economic conditions are different
  - Concomitant illness and medications

Clioquinol induced SMON in Indians

- 10,000 cases of SMON in Japan over 15-years
- India:
  - A retrospective study of 5,168 records (1967-71)
  - ✓2 cases compatible with SMON
  - A prospective study (1972-77)
  - ✓ 7 cases of SMON – only One definite
- "Drug **not** banned for adults"

(Wadia NH. Some observations on SMON from Bombay. J Neurol Neurosurg Psychiatry. 1977 ;40(3):268-75.)

Drugs banned elsewhere…. available in India

- Nimesulide - Hepatic failure
  (Not for children under 12 years of age)
- Phenylbutazone - Blood dyscrasias
- Metamizole - Agranulocytosis
- Quiniodochlor - Subacute myelo-optic neuropathy (SMON)

Drugs banned in India

- Cisapride - QT prolongation
- Gatifloxacin - Hypo/hyperglycemia
- Rosiglitazone - Adverse Cardiac events
- Sibutramine - Adverse Cardiac events
- Tegaserod - Heart Attack, stroke
- Rimonabant - Suicidal Ideation
- PPA - Hemorrhagic stroke

Pharmacovigilance in India

1986

ADR monitoring system for India proposed (12 regional centres

1997

India joined WHO-ADR monitoring programme (3 centres: AIIMS, KEM, JLN)

2004 – 2008

National Pharmacovigilance prog. (2 Zonal, 5 Regional, 24 Peripheral Centres)

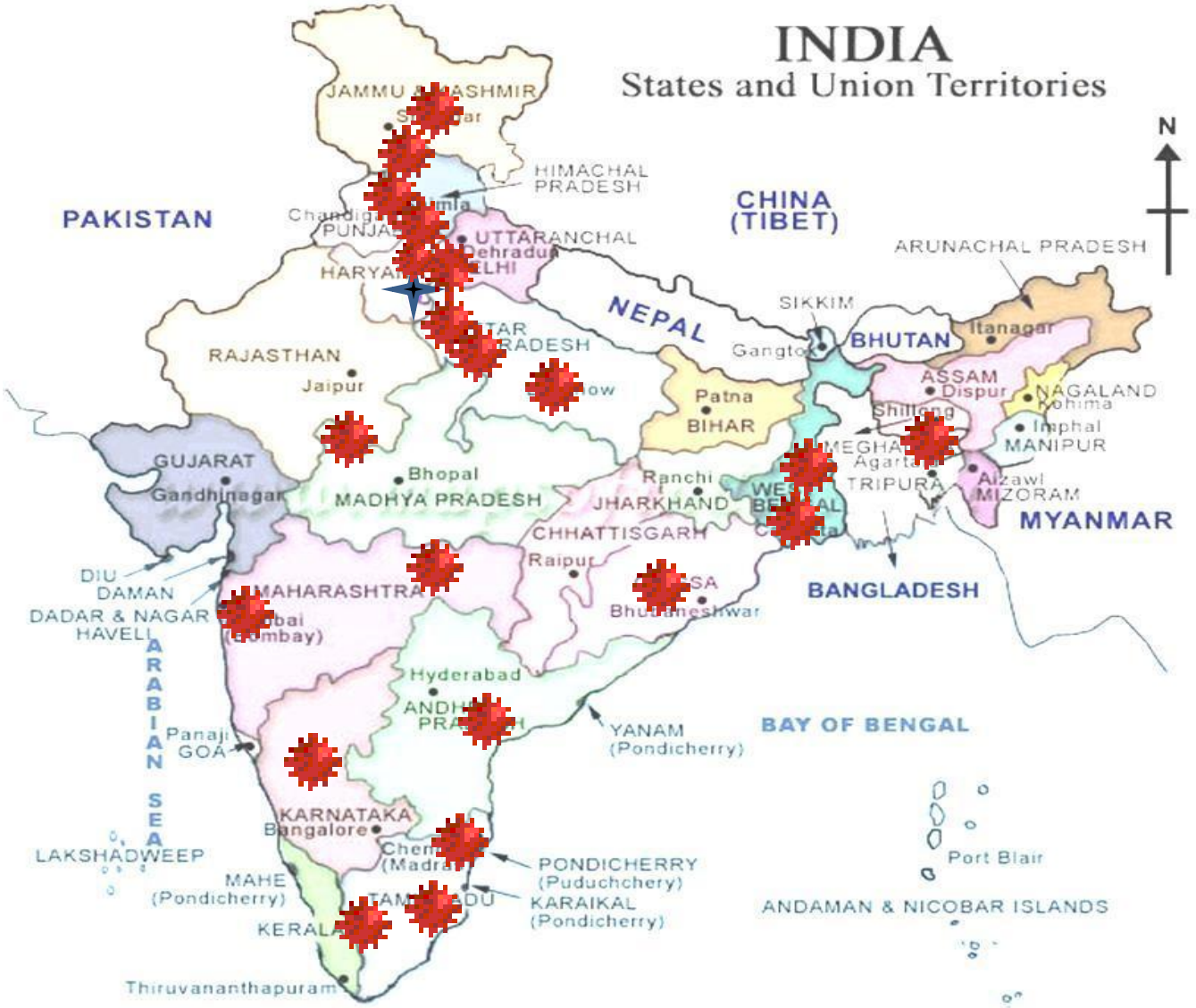
2010…

Pharmacovigilance Programme of India (PVPI)

Pharmacovigilance Programme of India (PVPI) was launched in July 2010.

Goal

To ensure that the benefits of use of medicine outweighs the risks and thus safeguard the health of the Indian population

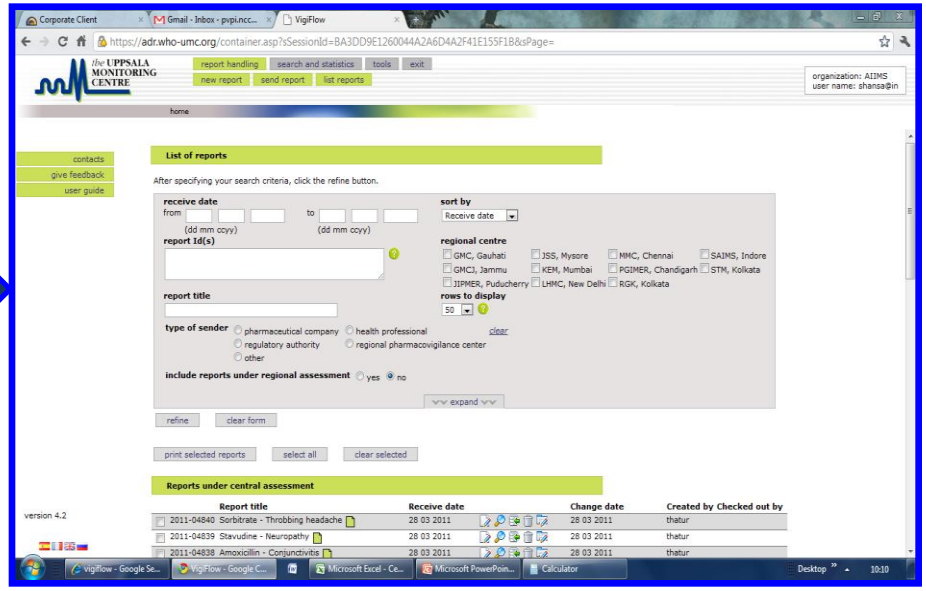


Centres in First wave of PvPI: 12 + 10 = 22

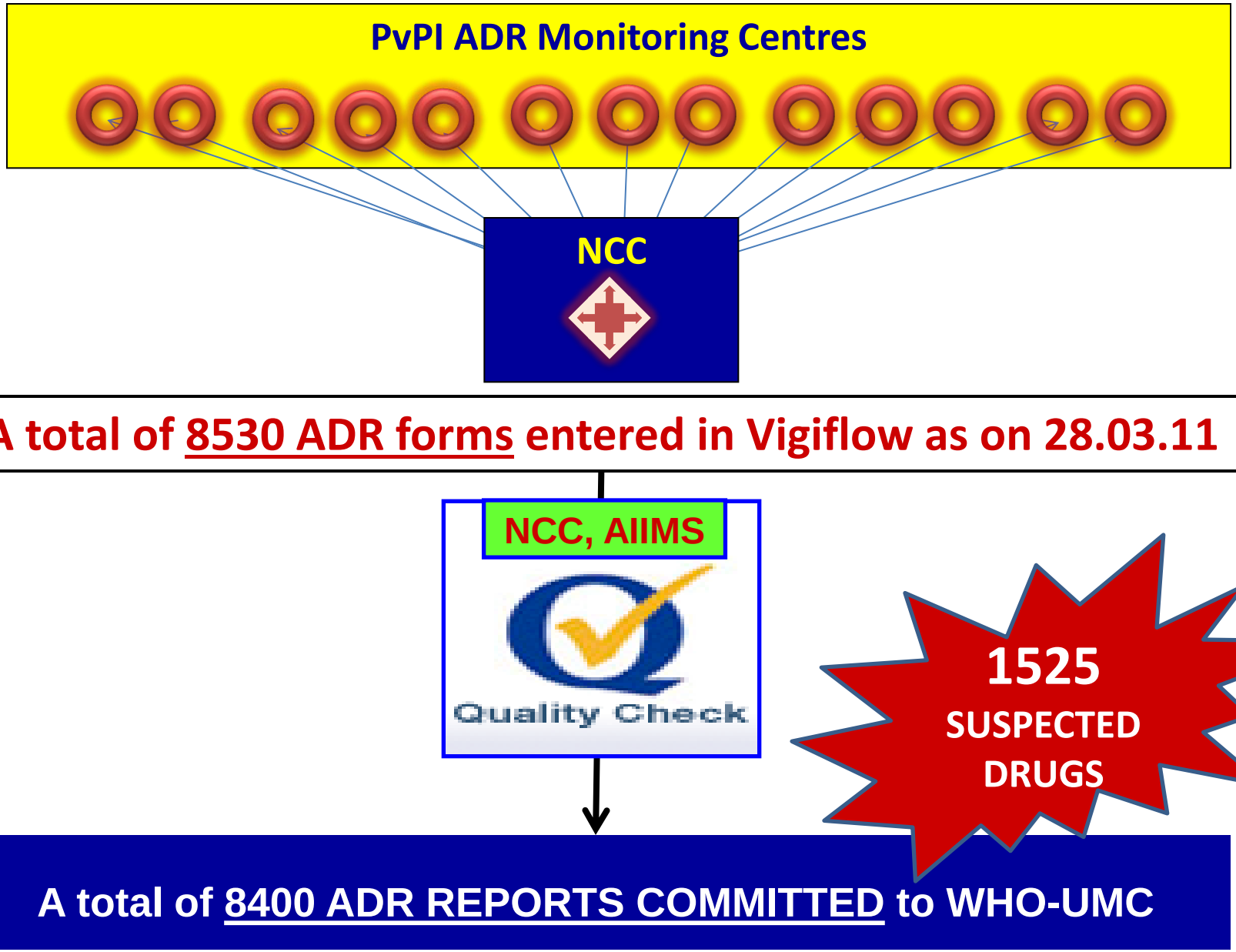
Current no. of centres in PvPI: 22 + 38 = 60

Pharmacovigilance activities done under National Coordinating Centre at AIIMS

1201 ADR reports entered in Vigiflow by NCC



7329 ADR reports entered in Vigiflow by ADR Monitoring Centres


PvPI ADR Monitoring Centres
NCC
A total of 8530 ADR forms entered in Vigiflow as on 28.03.11
NCC, AIIMS
Quality Check
1525
SUSPECTED
DRUGS
A total of 8400 ADR REPORTS COMMITTED to WHO-UMC

Version 2.1, January 29, 2010

PHARMACOVIGILANCE OF ANTIMALARIAL MEDICINES IN INDIA
with special emphasis on Artemisinin Combination Therapy (ACT)

National Institute of Malaria Research, National Vector Borne Disease Control Programme &
Department of Pharmacology, All India Institute of Medical Sciences, New Delhi

IMPORTANT INSTRUCTIONS

- The completely filled form should be sent to:

  Coordinator, National Pharmacovigilance Programme, Department of Pharmacology, Room no. 4012, 4th floor, Teaching Block, All India Institute of Medical Sciences, Ansari Nagar, New Delhi – 110029
- Please note that Artemisinin combination therapy is not recommended in pregnancy in India.
- The adverse event reporting form should be filled in a clear and legible handwriting.
- The form has two parts.
  - Part A (treatment visit) of the form should be filled on the day when the treatment of a malaria patient is started.
    - Please mention all the malaria related symptoms along with their duration.
    - Specifically ask the patient for any other clinical events developing in 7 days before the visit which are not related to malaria and mention in the relevant section. E.g. Measles, ankle pain, tonsillitis etc
    - Pre-existing medical conditions should include a history of conditions like diabetes, hypertension, HIV, TB, liver/kidney/cardiac disease, allergies, alcohol, tobacco use.
    - At the time of this visit the patient must be asked to return between 7 – 15 days and should be given a follow up appointment (for filling up Part B).
  - Part B (follow up visit) of the form should be filled between 7 – 15 days after part A and not with the regular 3 day follow up.
    - If the type of follow up is other than the visit to centre/ home, mention in the space provided. It could be a telephonic follow up or a call to follow up (the patient could not be contacted after first visit)
    - Ask the patient for all the medicines that he/she consumed while on anti-malarial drugs for possible drug-drug interactions.
    - Details of worsening of an existing problem or a new event should include any adverse reaction that the patient developed after the last visit. Any such event should be described in detail along with the date of start, date of stopping, name of the medicine which in your view is responsible for the event and the outcome of this adverse event.
- All the medicine names should include pharmacological as well as brand name of the drug.
- The report should be sent immediately if the outcome of an adverse event is: death/ life-threatening/ persistent incapacity or disability/ caused or prolonged hospitalization.
- Your identity will remain confidential and this information will not be used for any medico-legal purposes.
- Submission of this form does not imply that the medicine or reporting person is responsible for the adverse event.
- This information will be analyzed and will contribute to promoting safe use of antimalarials.

For any query regarding filling up the forms/ suggestions contact:

Principal investigators

1. Dr. Neena Valecha, MD, Scientist F, NIMR, neenavalecha@gmail.com, 011- 25307402
2. Dr. Anup Anvikar, MD, Scientist D., NIMR, anvikar@rediffmail.com, 011 - 25307122
3. Prof. Y.K. Gupta, MD, Head, Dept. of Pharmacology, AIIMS, ykykgupta@gmail.com, 011-26593262

Study Coordinator

Dr. Pooja Gupta, MD, Senior Resident, Department of Pharmacology, AIIMS, drgupta.pooja@gmail.com, 011-26593664

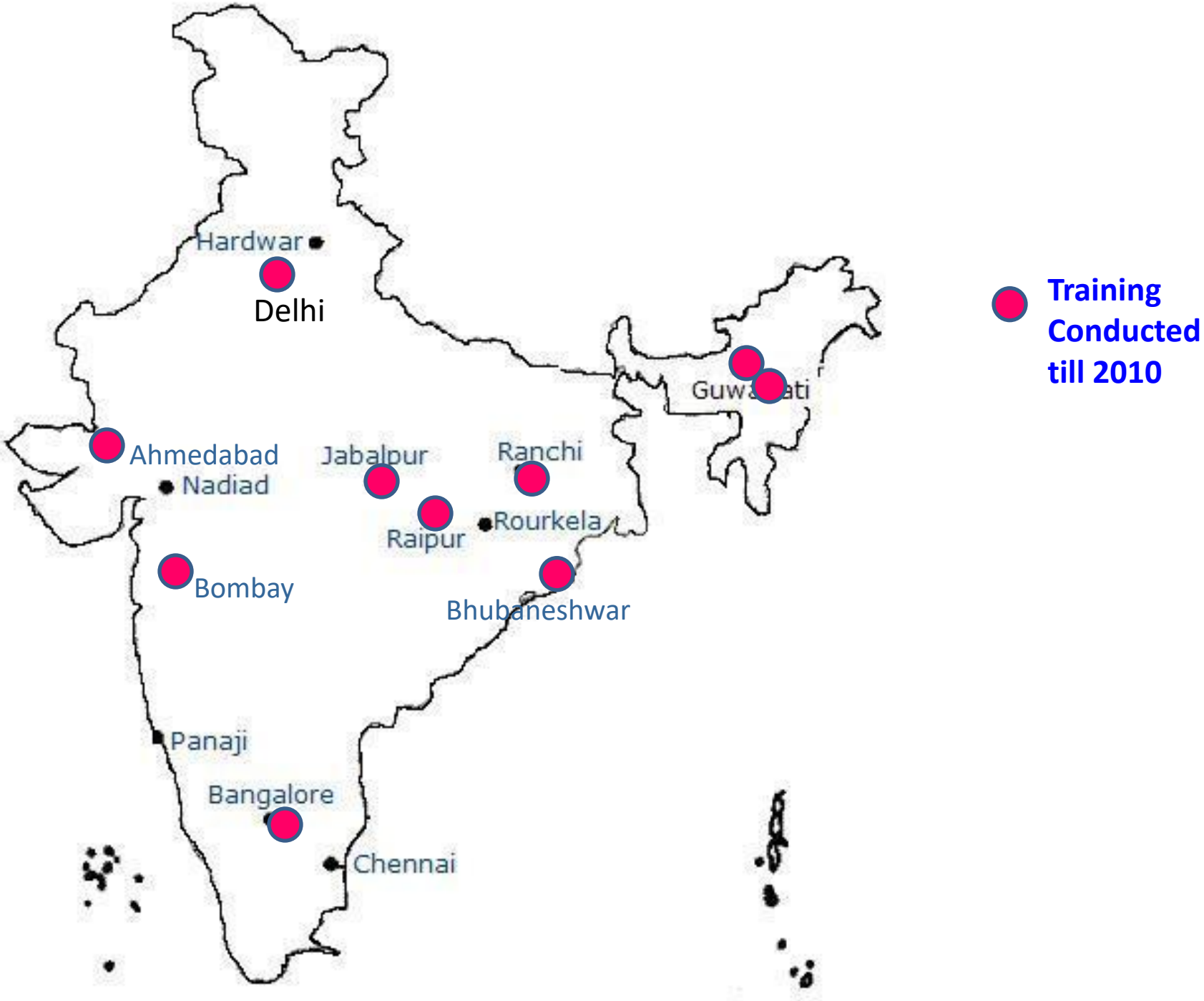
The form may also be photocopied and used.

PHARMACOVIGILANCE OF ANTIMALARIAL MEDICINES IN INDIA

With special emphasis on Artemisinin Combination Therapy (ACT)

National Institute of Malaria Research
National Vector Borne Disease Control Programme
Department of Pharmacology
All India Institute of Medical Sciences, New Delhi

Website: http://www.mrcindia.org
Email: malaria.safety.india@gmail.com


Hardwar
Delhi
Guwahati
Ahmedabad
Nadiad
Jabalpur
Ranchi
Raipur
Rourkela
Bombay
Bhubaneshwar
Panaji
Bangalore
Chennai
Training Conducted till 2010

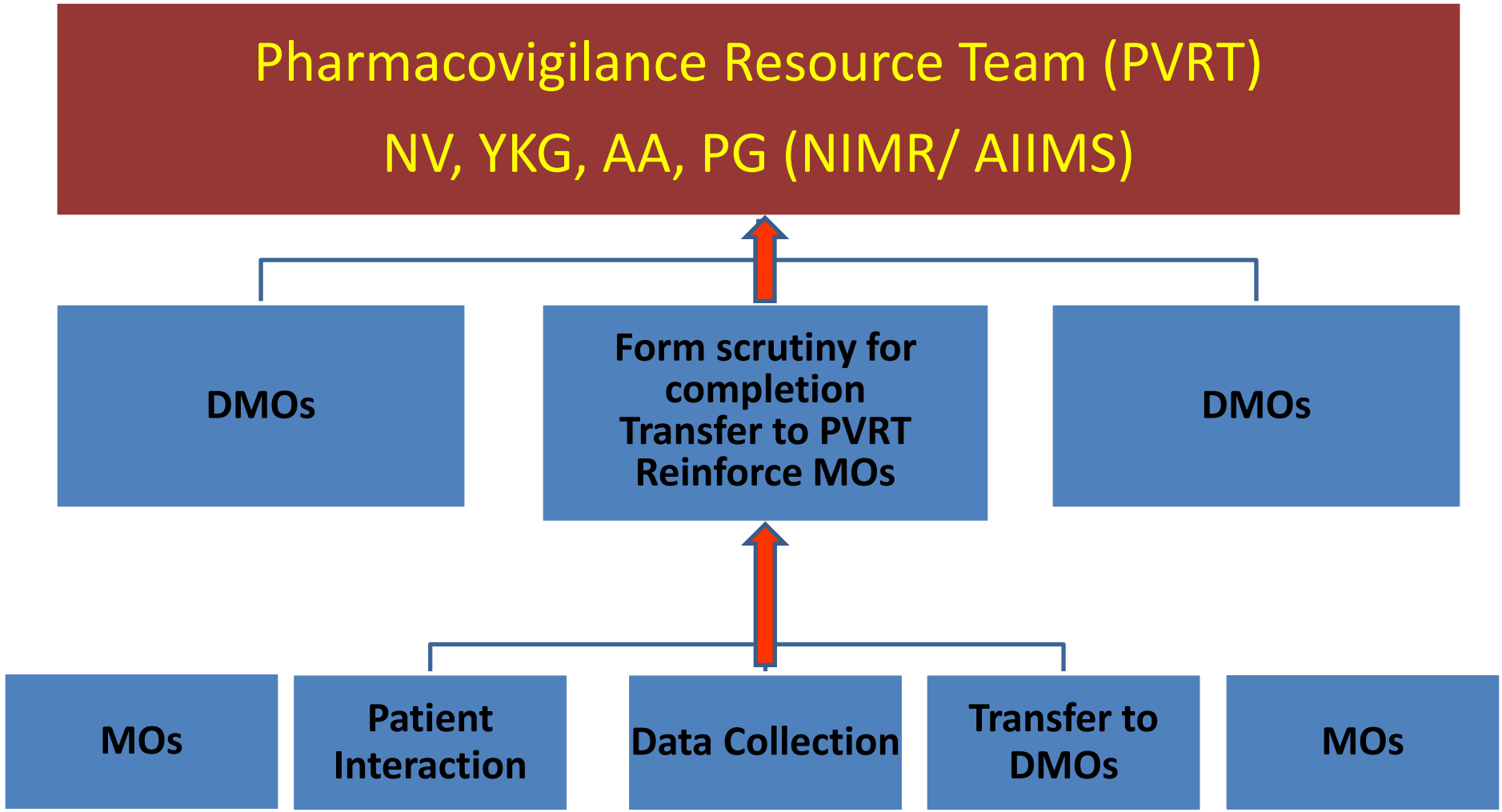

AIIMS
AIIMS


ORIENTATION MEETING OF DISTRICT
PROGRAMME OFFICERS ON QUALITY
ASSURANCE OF MALARIA LABORATORY
DIAGNOSIS AND PHARMACOVIGILANCE OF ANTIMALARIALS
Date : 10 April 2010
Dr. NEERU SINGH
Dr. V K GUPTA
Dr. K D BAGHEL
Dr. NEENA VALECHA
Dr. KALPANA BARUAH


REST ROOMS


05/04/2010

Data Flow


Pharmacovigilance Resource Team (PVRT)
NV, YKG, AA, PG (NIMR/ AIIMS)
DMOs
Form scrutiny for completion
Transfer to PVRT
Reinforce MOs
DMOs
MOs
Patient Interaction
Data Collection
Transfer to DMOs
MOs

Current Status

S.no.	City/ State	No of Forms	Total no. of ADR Reports
1	Gujarat	616	For the period Nov '09 -May' 11 1200 ADRs received at AIIMS Total Adverse Events: 42
2	Karnataka	207	
3	Mumbai	4	
4	Manipur	6	
5	Nagaland	16	
6	Meghalaya	10	
7	Mizoram	51	
8	Orissa	12	
9	Chattisgarh	5	
10	Madhya Pradesh	30	

Strategies adopted to boost reporting

- Monthly telephonic follow up with District Malaria Officers
- Personalized thank you emails to reporting Medical Officers
- Interesting study material related to vector borne diseases sent by email

Adverse Event Following Immunization (AEFI)

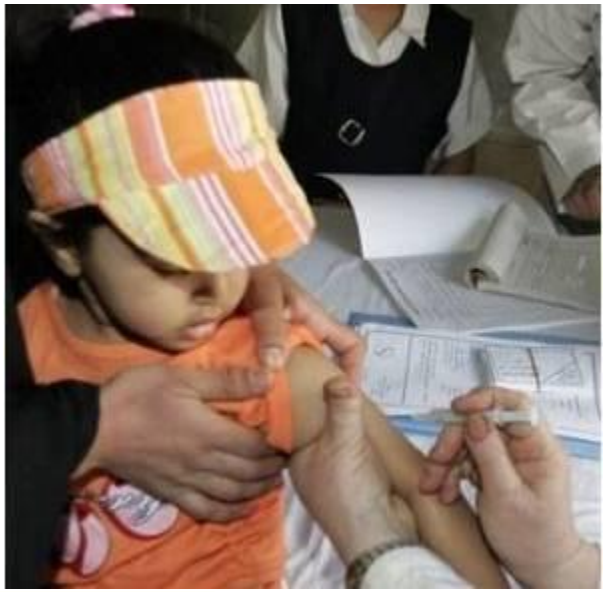
- A medical incident that takes place after an immunization which causes concern and is believed to be caused by immunization (WHO)

Adverse Events to HPV Vaccine

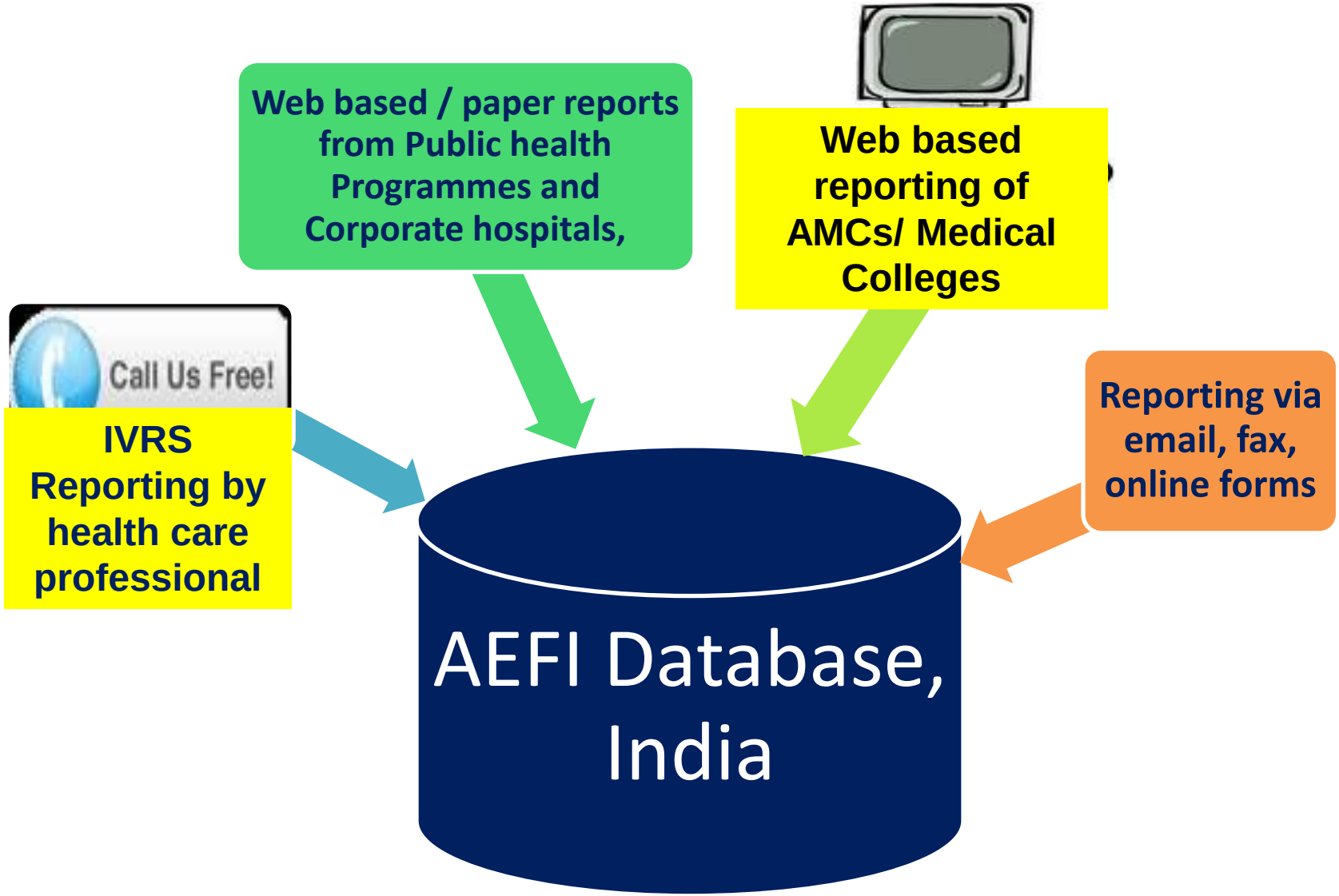
- HPV vaccine demonstrated to be safe in the premarketing clinical trials
- 7 deaths in India in one post-marketing study
  - Clear causality with the vaccine was not established
- Lessons learned in the process
  - Public distrust can adversely affect any healthcare programme
  - Timely addressing such concerns is crucial

Measles vaccination drives

- Clusters of deaths reported in India
  - Tamil Nadu, Assam, UP
  - Mostly due to programme error
  - Quality of the vaccines ??



Proposed System for AEFI in India



Integrated Medicine Management System **(IMMS at AIIMS)**

- To promote standard and generic drugs through the government hospitals
- Model being prepared by the AIIMS
  - Link with pharmacovigilance (Alerts)
- Major anticipated benefits
  - Monitor quality of drugs,
  - Minimize ADR, medication errors,
  - Prescription tracking

Partnering for Progress ..

Thank you