Explain the role of investigators, clinical trials.

Investigators: A person responsible for the conduct of the clinical trial at a trial site. If a trial conducted by a team of individuals at a trial site the investigator is the responsible leader of the team and may be called the principal investigator.

Role

1) Investigator's qualifications and agreements.
2) Adequate Resources.
3) Medical Care of trial Subjects.
4) communication with IRB / IEC.
5) compliance with protocol.
6) investigational product.
7) Randomization procedures and un-blinding.
8) Informed consent of trial subjects.
9) Records and reports.
10) Progress Reports.
11) Safety Reporting.
12) Premature termination or suspension of a trial.
13) Final reports.

1) Investigator's qualifications and agreements →

The investigator should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial should meet all the qualifications specified.

2) Adequate Resources →

The investigator should be able to demonstrate a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

3) Medical care of trial Subjects →

A qualified physician, should be responsible for all trial

related medical decisions.

4. Communication with IRB/IEC →

Before initiating a trial, the investigator should have written and dated approval/favorable opinion from the IRB/IEC for the trial protocol.

5. Compliance with protocol →

The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and if required by the regulatory authority and which was given approval/favorable opinion by the IRB.

6. Investigational product →

The investigator and/or a pharmacist or other appropriate individual who is designated by the investigator.

7. Randomization procedures and un-blinding →

The investigator should follow the trial's randomization procedures, if any and should ensure that the code is broken only in accordance with the protocol.

8. Informed consent of trial subjects →

Prior to the beginning of the trial, the investigator should have the IRB/IEC written approval/favorable opinion of the written informed consent.

9. Records and Reports →

The investigator should ensure the accuracy, completeness legibility and timeliness of the data reported to the sponsor in the CRF.

10. Progress Reports →

The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently if requested by the IRB/IEC.

Clinical Research Associate (CRA)

Also called a clinical monitor or trial monitor, is a health-care professional who performs many activities related to medical research, particularly clinical trials.

Clinical research associates collect and organize data obtained during studies and trials conducted in fields such as biotechnology and pharmaceuticals

CRA's ensures compliance & protocol.
Check clinical site activities
make on-site visits
reviews eRFs
Communicates & investigators.

As per ICH - GCP guidline →

- Monitors should be appointed by sponsor. Monitors should be trained, have scientific and clinical knowledge.
- A monitor's qualifications should be documented
- Monitors should be familiar ε

Monitor's Responsibilities:

1. Acting as main line communication b/w sponsor and investigator.
2. Verifying that investigator has adequate qualification and resources facilities including — laboratories
   - equipment
   - staff
   - adequate safety.
3. Investigational product that storage time and condition are acceptable.
4. That investigational products are supplied only to subjects who are eligible to recieve it and at protocol specified dose.
5. Subjects are provided ε necessary instruction on using, handling, storing.
6. Disposition of unused investigated products at trial sites complies ε applicable regulatory and is in accordance ε sponsor.
7. Verifying that investigator follows approved protocol and all approved a mendment.
8. Verifying that written informed consent was obtained before each subjects

Participation in trial.

9. Ensuring that investigator recieves.
10. Ensuring that investigators trial staff are performing.
11. Verifying the investigator is enrolling only eligible subjects
12. Reporting the subject recruitment rate.
13. Verify documents and trial records are accurate complete and upto date.
14. Verify that investigators provides all required reports, notification, application and these documents are accurate.
15. Checking the accuracy and completeness of CRF entries, source documents and related records.
16. Any dose and therapy modifications are well documented for each trial subject.
17. Adverse event, contamitant medication and intercurrent illnesses are reported ☆ protocol on CRFs.

Regulatory Authority :

Introduction :

National regulatory authorities overdose and monitor the development of new drugs.

1. In usA FDA oversees new drug development.
2. In europe european agency for the evaluation of medicinal products (EAEM)
3. In Japan the Ministry of Health abour and welfare.
4. In china the state drug administration
5. In India DCGI, CDSCO, SLA, NPAC, CDA.

Objective :

The overall objective of a drug regulatory authority (DRA) is to ensure that;

1. Medicinal products are of acceptable quality safety and efficacy.

2. Manufactured and distributed in ways which ensure their quality they reach the patient / consumer and their commercial promotion is accurate.

Roles and responsibility :

1. Regulatory affairs officers ensure the appropriate licensing marketing and legal compliance of pharmaceutical and medical

Products in order to control the safety and efficacy of products.

2. They combine their knowledge of scientific legal and business issues to ensure product which are developed manufactured or distributed by a wide range of companies meet the required legislation.

3. They advise on and coordinate the approval and registration of pharmaceuticals veterinary medicines complementary medicines chemicals, pesticides, therapeutic devices and other products.

4. Regulatory affairs officers are the crucial link b/w their company, its products and regulatory authorities.

Responsibilities:

1. Ensuring that a company's products comply with the regulations.
2. Keeping abreast of international legislation guide lines and customer practices.
3. Collecting and collating a wide range of information.
4. Keeping up to date with a company's product range.
5. Developing and writing clear arguments and explanations for new product licenses and license renewals.
6. preparing submission of license variations and renewals to strict deadlines.
7. Monitoring and setting timelines for license variations and renewal - approvals.

8. Working with specialist computer software and resources.
9. Writing clear, accessible product labels and patient information leaflets.
10. planning and developing product trials and interpreting trial data.
11. Advising scientists and manufactures on regulatory requirements.
12. project managing teams of colleagues involved with the development of new products.
13. undertaking and managing regulatory inspections.
14. Reviewing company practices and providing advice on changes to systems.
15. liaising with and making presentations to regulatory authorities.
16. Negotiating with regulatory authorities for marketing authorization.
17. Specifying storage, labeling and packaging requirements.

AUDITORS:

Audit:

A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities where conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good clinical pratice (GCP) and the applicable regulatory requirements.

Audit Certificate:

A declaration of confirmation by the auditor that an audit has taken place

Audit Report:

A written evaluation by the sponsor's auditor of the results of the audit.

Audit trail:

Documentation that allows reconstruction of the course of events.

Selection and Qualification of auditors:

a- The sponsor should appoint individuals who are independent of the clinical trials systems to conduct audits.

b- The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly An auditors qualification

should be documented.

Responsibilities of auditors:

The sponsor should specific the roles and responsibilities of the auditor before starting to conduct an audit so as to ensure fair and smooth performance of the audit. The auditor is responsible for maintaining the confidentiality of information obtained during an audit, planning and conducting the audit and reporting the audit results.

Purpose of Audit:

To evaluate the trial conduct and compliance with

i- Quality systems.
ii) SOPs
iii) Protocol
iv) Good clinical pratice and
v) other applicable regulatory requirements.

What to audit:

organization and personnel responsibilities and functions.

Qualification, training and adequacy of staff list of monitors list of all investigators.

Drug supply agreement, clinical trial (site) agreement, other services agreement and material transfer agreement.

Quality management system investigational drug manufacturing, packaging, labeling and coding

of the IP (including placebo and active comparator where applicable) in accordance with Applicable GMP ~~standard~~ standards labeling requirements.

- Drug product accountability.
- IRB/IEC.
  - responsibility.
  - composition
  - functions
  - operations.
  - Procedures
  - Records.

Essential documents:

- Investigator's brochure
- signed protocol and amendments.
- Advertisements for subject recruitment
- Informed consent forms approved by IRB/IEC to requirements.
- Financial aspects of the trial.
- Case report forms.
- Serious adverse events reporting.
- instructions for handling
- shipping records.

Bio analytical laboratories
computerized systems
Statistical components

How to execute an audit:

The execution of audit process is divided into three steps.

i) Before the audit.
ii) During the audit.
iii) After the audit.

Before the audit process:

Auditor contacts the site to arrange for a mutually acceptable date and time for an audit to be conducted.

A detailed agenda of an audit is informed to the CRC and also about the documents to be checked during an audit.

Auditor previews the protocol, CRF, local regulations and guidelines project specific guidelines, relevant SOPs to be aware of the trial

During the audit Process:

① opening meeting.
- An introductory meeting between the auditor and the site team.
- Auditor briefs the scope and procedures to be followed during the audit.
- An opportunity for trial team members to communicate with the auditor.

Review documents and collating information.
Audit observations (documents all observations)

After the audit Process:

Auditor should issue the audit report within 28 days of the final audit activity.
He makes clinical research personnel aware

of the findings to their activities, and findings are classified as critical, major and minor.

① Prevention / corrective action it is should accompany the report.

A formal audit response should be prepared and submitted by the trial team to the concerned personnel after the corrective measures have been taken.

Following the satisfactory responses to the audit, auditor issues an audit certificate confirming that audit has taken place and filed in clinical trial report and also submitted to regulatory authorities.

Protocol:

Written detailed procedure for conducting the research study and collecting data.

The contents of a trial protocol should generally include the following topics however, site specific information may be provided on separate protocol page or addressed in a separate agreement and some of the information listed below may be contained in other protocol referenced documents such as investigator's brochure.

1. General information:

1. protocol title protocol identifying number; and date. Any amendment should also bear the amendment number and date.
2. Name and address of the sponsor and monitor (if other than the sponsor)
3. Name and title of the person authorized to sign the protocol and the protocol amendment for the sponsor.
4. Name, title, address and telephone number of the sponsor's medical expert for dentist when appropriate for the trial.
5. Name and title of the investigator who is responsible for conducting the trial and the address and telephone number of the trial site.
6. Name, title address and telephone number of the qualified physician who is responsible

for all trial-site related medical decisions.

7. Name and address of the clinical laboratory and other medical and/or technical department and/or institutions involved in the trial.

2. Background information:

i) Name and description of the investigational product.

ii) A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

iii) Summary of the known and potential risks and benefits, if any to human subjects.

iv) Description of and justification for the route of administration, dosage, dosage regimen and treatment period.

v) A statement that the trial will be conducted in compliance with the protocol GCP and the applicable regulatory requirement(s).

vi) Description of the population to be studied

vii) References to literature and data that are relevant to the trial and that provide background for the trial.

3. Trial objectives and purpose:

A detailed description of the objectives and purpose of the trial.

4. Trial design:

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design.

A description of the trial design, should include —

i) A specific statement of the primary endpoints and secondary end points if any to be measured during the trial.

ii) A description of the type / design of trial to be conducted and a schematic diagram of trial design, procedures and stages.

iii) A description of the measures taken to minimize / avoid bias including a- randomization b- blinding.

iv) A description of the trial treatment and the dosage and dosage regimen of the investigational product also include a description of the dosage form packaging and labelling of the investigational products.

v) The expected duration of subject participation and a description of the sequence and duration of all trial period including follow-up if any.

vi) A description of the stopping rules or discontinuation criteria for individual subject part of trial and entire trial.

vii) Accountability procedures for the investigational product including the placebo and comparator if any.

viii) Maintenance of trial treatment randomization codes and procedures for breaking codes.

ix) The identification of any data to be recorded directly on the CRFs and to be considered to be source data.

5. Selection and withdrawal of subjects:
   i) subject inclusion criteria.
   ii) subject exclusion criteria.
   iii) subject withdrawal criteria
      a) When and how to withdraw subjects from the trial.
      b) The type and timing of the data to be collected for withdrawn subjects.
      c) whether and how subjects are to be replaced.
      d) The follow up for subjects withdrawn from investigational product treatment.

6. Treatment of subjects:
   i) The treatment to be administered including the names of all the product the dose the dosing schedule the route/mode of administration and the treatment period including the follow up period for subjects for each investigational product treatment/trial treatment group/arm of the trial.
   ii) Medication/treatment permitted and not permitted before and/or during the trial.
   iii) procedures for monitoring subject compliance

7. Assessment of efficacy:

i) Specification of the efficacy parameters

ii) Methods and timing for assessing, recording and analysing of efficacy parameters.

iii) Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

iv) The type and duration of the follow-up of subjects after adverse events.

9. Statistics:

i) A description of the statistical methods to be employed including timing of any planned interim analysis (ses)

ii) The number of subject planned to be enrolled in multicentre trials the numbers of enrolled subjects (projected for each trial site should be specified. Reason for choice of sample size including reflections on the power of the trial and clinical justification.

iii) The level of significance to be used.

iv) criteria for the termination of the trial

v) Procedure for accounting for missing, unused and spurious data.

vi) Procedures for reporting any deviation from the original statistical plan.

10. Direct access to source Data/documents:

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator / institution

will permit trial-related monitoring, audits IRB/IEC review and regulatory inspection providing direct access to source data / documents.

11. Quality control and Quality assurance:

12. Ethics

Description of ethical considerations relating to the trial.

13. Data handling and record keeping.

14. Financing and insurance:

Financing and insurance if not addressed in a separate agreement.

15. Publication policy →

publication policy if not addressed in a separate agreement.

16. Supplements.

Case Report Form (CRF)

Definitions:

Case report forms are the research instruments or tools designed to collect the data that are necessary to answer the research questions of a specific protocol.

Good clinical practice (GCP) - standard developed by the international conference on harmonization defines CRF as the printed, optical or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

Generally, data recorded on a CRF include basic subject - specific socio demographic information such as birth date, ethnicity race, education level, data from study specific examinations, measurements or specialty tests data abstracted from the subject's medical record or other source documents such as ambulatory and in-patient records. Laboratory results other tests and special procedure design of research survey and questionnaires require special considerations that are addressed in the CRC Research Practice guideline for developing surveys.

Purpose of CRFs:

i) Capturing all protocol - required information
ii) Facilitates data collection and entry.
iii) Benefits data management.
iv) Benefits statistical analysis.
v) Simplifies database design and data validation processes as well as manipulation of data during statistical analysis.

CRFs Development process:

Because of the significance of the CRF in the successful completion of the clinical trail and the importance of its design to the different contributions that endeavour a team-based approach to CRF design and review is highly recommended.

- CRF designer
- Medical advisor.
- clinical moniton.
- Data entry leader.
- Data manger
- statistician.

prior to designing the CRF, the investigator and study team should carefully review the study protocol and do the following:

1. Develop the list of variables that need to be collected. use the research questions specified in the IRB - approved protocal to guide development of the variable list. For each ~~reserch~~ research question make a list

16. SAFETY MONITORING IN CLINICAL TRIALS

INTRODUCTION:

1. Clinical trials are a cornerstone in medical advances; hence there is a progress in the design and conduct of a clinical trial.
2. This lead to an increased awareness of ethical issues and safety monitoring.
3. Hence a system should be there to ensure the safety of participants.
4. The establishment of a **Data safety monitoring boards (DSMB)** is required for clinical trials, involving potential risks to the patients.

According to the principles of ICH-GCP guidelines:

- The rights, safety and well being of the trial subjects are the most important considerations.
- Safety Monitoring is done by:

1. Investigator
2. IRB/IEC`s
3. Sponsor
4. Monitor

1. Investigator - responsibility:

During and following subject participation in a trial, the investigator should ensure that the adequate medical care is provided to the subjects for any adverse events, related to the trial [ICH-GCP 4.3.2]

2. IRB/IEC - responsibility:

- An IRB/IEC should safeguard the rights, safety and well being of all trial subjects.[ICH-GCP 3.1.1]
- The IRB IEC should conduct continuing review of each ongoing trial, at definite intervals. At least once per year.

3. Sponsor - responsibility:

Sponsor may consider establishing an independent data monitoring committee (IDMC) (or) DSMB to assess the progress of a clinical trial, which includes the safety data and to recommend to the sponsor, whether to continue, modify or stop a trial [ICH-GCP 5.5.2]

4. Monitor - responsibility:

Determining whether all adverse events are properly reported within the time period required by:

1. GCP
2. Protocol
3. IRB/IEC
4. Sponsor and
5. Applicable regulatory requirements. [ICH-GCP-5.18.4]

SAFETY MONITORING IN DIFFERENT PHASES OF CLINICAL TRIALS

Phase-I:

Experimental drug given in a small group of people (20-80) to evaluate its **safety, determine a safe dosing range, identify side effects.**

Phase-II:

Experimental (study) drug is given to a large group of people (100-300) to see **its effectiveness and to further evaluate safety.**

Phase-III:

Experimental drug is given to a large group of people (1000-3000) to confirm its effectiveness, monitor side effects, and collect information for safety.

Phase-IV:

1. Post marketing studies, gives additional information includes drug risks, benefits, and optimal use.
2. For drugs being studied under investigational new drug application [INDA], the FDA published a regulation, establishing a new safety reporting paradigm.
3. According to this clinical investigator and sponsor have to be more responsible in reporting and analysis of serious, unexpected events that might be caused by drug.

Types of Monitoring

1) Central monitoring.

- Determination of key eligibility criteria through collection of:
  - Consent forms
  - Scans
  - Pathology reports

- Statistics
  - Unusual patterns of data.

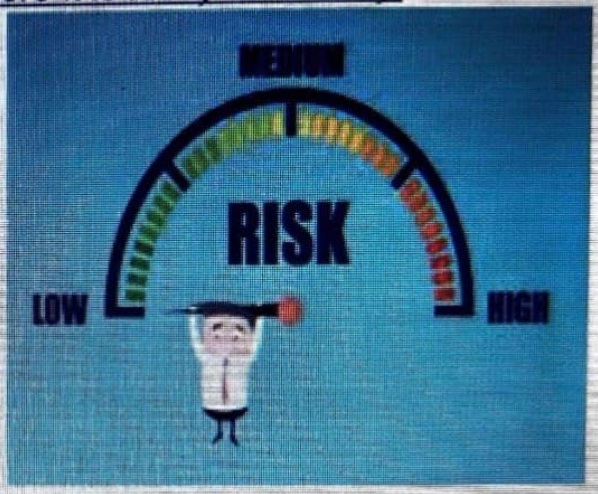
ICH GCP 5.18.3

Types of Monitoring

2) Risk Based monitoring. *ICH GCP 5.18.3*

❑ Limited resources should be used to where it is really necessary. High risk part.
- For subject protection
- For reliability of trial results
- For protection of future patients

❑ Risk-based approach! (6 Rs)
1- Risk Identification
2- Risk Evaluation
3- Risk Control
4- Risk Communication
5- Risk Review
6- Risk Reporting



ICH GCP Sections 2.13, 5.0 (, 5.20.1)

Types of Monitoring Cont..

3) **On site Monitoring.**
- Staff training
- Access to necessary documents
- Confirm pharmacy and lab resources in place
  * Count study drugs
- Adherence to protocol and GCP
- Check medical records
  * Consent forms
  * Eligibility
  * AEs
- Source Data Verification (SDV)

Monitoring Process Continued..

1) **Before** Monitoring Visit :

- Review the status of data entry
- Review action item from last visit
- Review regulatory binder
- Check PI & site staff availability
- Get the internal team approval
- Send confirmation/agenda of monitoring visit

Monitoring Process Continued..

2) **During** Monitoring Visit.

- The monitor will assess or discuss:

❖Site, staffing, research labs or other facilities
❖Regulatory file and study records
❖Clinical procedures if possible or appropriate
❖Any problems and issues identified
❖Debrief at end of visit

Monitoring Process Continued..

2) During Monitoring Visit.

- The monitor will assess or discuss:

- ❖Site, staffing, research labs or other facilities
- ❖Regulatory file and study records
- ❖Clinical procedures if possible or appropriate
- ❖Any problems and issues identified
- ❖Debrief at end of visit

Monitoring Process Continued..

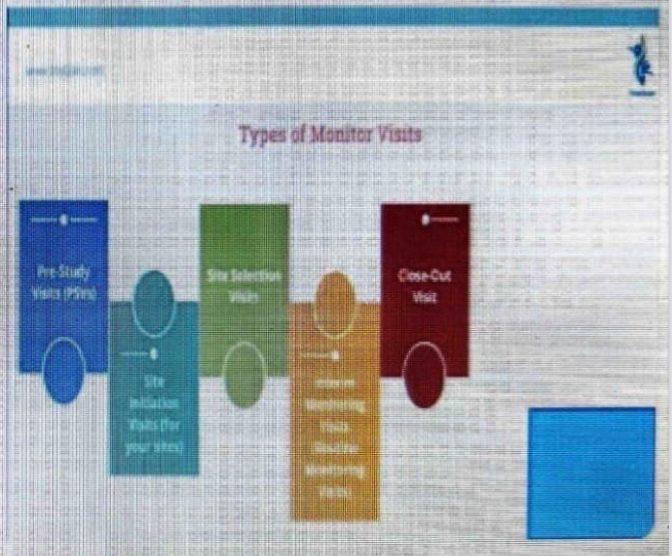
3) After Monitoring Visit.

The monitor will.....

- ❖Complete site visit report
- ❖Submit the report to the sponsor

4 Types Monitoring Visits

1) Site assessment(pre trial) Visit
2) Site initiation Visit
3) Routine(interim) visit
4) Close Out Visit



SPONTANEOUS REPORTING

- Spontaneous reporting system is a passive surveillance system.
- Health professionals are encouraged to report adverse reactions which they believe to be drug-related directly to:
    1. The regulatory authorities (or)
    2. The company making the suspected product on a voluntary basis.
- Spontaneous reporting system has three steps:
    1. Data Acquisition
    2. Data assessment
    3. Data interpretation

1. Data acquisition:

Which depends largely on the input of information derived from the reports submitted by the health professionals, who have encountered, what they suspect is an ADR.

2. Data assessment:

Involves assessment of the individual case reports and assessment of pooled data obtained from various sources, such as the international database of the WHO.

3. Data interpretation:

Based on the available data and assessments made, a signal related to the adverse reaction may be generated.

Pharmacovigilance aims at detecting adverse effects of marketed drugs. It is generally based on a spontaneous reporting system (SRS) that consists of the spontaneous reporting, by health professionals, of events that are supposed to the adverse effects of marketed drugs.

- Automated signal generation methods have been proposed.
- The success or failure of any Pharmacovigilance activity depends on the reporting of suspected adverse reactions.

Different countries have different adverse drug reporting forms (or) systems. Those are:

- India - Suspected Adverse Drug reaction reporting form.
- UK - 'Yellow card' since 1964.
- Australia - 'Blue card' since 1964.
- United States - 'Med watch'.
- Form FDA 3500 - Voluntary reporting.
- Form FDA 3500A - Mandatory reporting.

- Studies in pharmacoepidemiology are intended to be either "hypothesis generating" or "hypothesis testing".
- Hypothesis-generating studies, with a recently marketed drug, aim to detect unexpected adverse drug reactions.
- Hypothesis testing studies, aim to prove whether any suspicious that may have been raised are justified.

Hypothesis - Generating studies:

They are generally done by two methods:

- Spontaneous ADR reporting.
- Prescription event monitoring (PEM).

SPONTANEOUS ADR REPORTING

- Spontaneous reporting is defined as "A system whereby case reports of adverse drug reactions or events are voluntary submitted by health professionals and pharmaceutical companies to the National Pharmacovigilance Centre" (NPC).
- Doctors (in some countries, other health care professionals and patients as well) are provided with forms, upon which, if they detect any suspected adverse drug reactions, they can notify it to the "central authority".
- In the United Kingdom, the 'yellow card' has been used for this purpose since 1964.
- The 'blue card' system is used in Australia and Malaysia.
- In the United States, the "Med watch" form is used, and is made broadly available to health professionals to encourage reporting.

ADR reporting in India:

For the purpose of reporting ADR's:

1. National Pharmacovigilance program was initiated.
2. Central Drugs Standard Control Organization (CDSCO) was coordinating 2 zonal centers, 5 regional centers and 28 peripheral centers are established for monitoring ADR reporting in India.

PHARMACOVIGILANCE PROGRAM OF INDIA

- CDSCO Directorate General of Health Services, under the aid of "Ministry of Health and Family Welfare", Government of India in collaboration with "Indian Pharmacopoeia commission, Ghaziabad (U.P) has started Pharmacovigilance program for protecting the health of the patients by assessing drug safety in India.
- Indian pharmacopoeia commission (IPC), Ghaziabad is functioning as a National Coordinating centre (NCC) for Pharmacovigilance Program of India (PVPI).
- 150 ADR Monitoring centers, were established in various medical institutions or hospitals across India to monitor and collect ADR reports under NCC-PVPI.

What to report:

- PVPI encourages all types of suspected adverse drug reactions reporting, whether they are known, unknown, serious or non serious, etc.
- Adverse drug reactions related with the use of allopathic medicines, vaccines, traditional medicines, medical devices, contrast media, etc. can be reported.

Where to report:

- All health care professionals (clinicians, dentists, pharmacists, nurses) and patients or Consumers can report ADR's to NCC or AMCs.
- The pharmaceutical companies can also send individual case safety reports for their product to NCC.

Advantages

- Calculation of incidence density
- Carried out on a national scale
- Comparison of 'reasons for withdrawal' and incidence density
- Outcome of exposed pregnancies
- Signal generation and exploration
- Delayed reactions can be detected
- Disease investigation

Disadvantages

- No method of measuring compliance
- No method to determine the non-prescription medication
- Non-return of green forms
- Does not extend to hospital monitoring
- Data collection is an operational difficulty