

ADVERSE EVENTS REPORTING

INTRODUCTION

Pharmacovigilance has always been considered a critical activity by almost all the key stake holders, associated with drugs, and its high place in organizational priorities has never been questioned. From time to time , episodes like thalidomide tragedy (1962) and cardiovascular risks posed by COX 2 inhibitors(2005), only add emphasis to this ever evolving medico-regulatory discipline.

Traditionally speaking , the science of pharmacovigilance has been a discipline more focused on the post marketing or post authorization period. As a part of ‘Risk Management Tool’ it has not only an important role to play in patients safety , but it has also assumed astronomical significance , to safeguard pharma industry against possible loss of revenue through damaging litigations and declining share value.However,as biological sciences have evolved, pharmacovigilance has also become an integral part of new drug development process. The new regulations require that they would be marketing authorization holders submit in the application dossier, a comprehensive review of the safety profile of the new drug , and how the potential risks will be further investigated and minimized during life cycle of medicines.

Most of the regulations that describe safety reporting from Clinical trials (CTs) focus on the expedited reporting of the individual case safety reports (ICSRs).ICH guidelines E2A which is generally considered the standard for the information to be sent, stipulates that sponsors should submit suspected adverse drug reactions that are both serious and unexpected to the regulators within 7 or 15 calendar days in an appropriate format.

Expedited single case reports from Clinical trials are accepted by majority of the Regulatory Authorities (RAs) on the CIOMS I or similar form. With the adoption of ICH guidelines E2B² and then E2B (M)³, which define standard data elements for electronic ICSRs, some RAs have begun to require the electronic submission of expedited reports in the post marketing scenario. More recently, the European Union (EU) and Japan have begun requiring electronic submission of expedited reports from CTs as well.

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While the time frames and reporting criteria that are: Suspected, Unexpected, Serious, Adverse, Reactions (SUSARs) for expedited reporting are mostly consistent across the ICH regions, there are authorities that require expedited reporting of suspected SADR, regardless of “expectedness”.

REQUIREMENTS FOR DIVERSIFIED EXPEDITED REPORTING

COUNTRY

US	SUL(Serious Unexpected Local)+ SUF(Serious Unexpected Foreign)
UK	SUL+SUF
Japan	SUL+SEL(Serious Expected Local)+SUF, also SEF if fatal or life threatening
France	SUL+SUF+SAEs having potential effect on trial designs (if studied in France)

As evident from the table, it is only “SUSARs”, are eligible for expedited reporting to the regulators in the above named countries, with the lone exception of Japan. Such regulation then pre-empt submission of weird unrelated cases, such as hip fracture, nerve injury involving machine accident ,enteric fever , to the regulators.

On the international front the Council for the International Organizations of Medical Sciences(CIOMS) , which , has proposed common policies for international postmarketing drug, adverse event reporting over the last 20years,recently moved to consider surveillance and safety reporting related to Clinical trials .Recently the CIOMS VI working group on managing safety information from clinical trials of medicinal products issued a final report offering recommendations for implementing common safety information reporting systems around the world. The report addresses expedited and periodic safety reporting and draws from the provisions in ICH documents, World Health Organization guidelines, and relevant EU directives and guidelines.

The report advises the research community to replace the current practice of sending large numbers of individual case reports to IRBs and IECs. Sponsors instead should submit “periodic and ad hoc communications” to investigators and ECs , with expedited communications focusing on “significant new safety information” that has “implications for the conduct of the clinical trial”. This approach follows the European policy of expedited reporting of serious and unexpected suspected adverse reactions (SUSARs), but still leaves it to investigators to decide what events warrant more aggressive reporting.

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Spontaneous reporting and Periodic Safety Update Reports(PSURs)form the backbone of the traditional ,post marketing surveillance activities throughout the pharma world.US FDA’s Med Watch forms and MHRA’s ‘Yellow Cards’ have almost become synonyms with spontaneous reporting .While US FDA recommends voluntary spontaneous reporting of all serious suspected ADRs through form 3500A, for health care professionals, it makes such reporting mandatory for the marketing Authorization Holders (MAHs) and draws very stringent timelines and reporting requirements.

The International expedited reporting requirements, in post authorization era are summarized in the table below:

REQUIREMENTS FOR INTERNATIONAL EXPEDITED REPORTING

COUNTRY

<u>US</u>	SUL(Serious Unexpected local)+SUF (Serious Unexpected Foreign)
<u>Canada</u>	SUL+SEL+SUF
<u>UK</u>	SUL+SEL(within MS)/SUF +SEF (from other EU)/SUF (Non EU)
<u>Japan</u>	SUL+SEL +SUF + Non- Serious Unexpected Local(NUL)
<u>France</u>	SUL+SEL(Within MS)/SUF (NON EU)

All other adverse events /reactions , which are not reported to regulators , in an expedited manner are included in periodic clinical trial reports (in case of pre-marketed development phase)and for marketed products in form of PSURs.A PSUR is “a formal, structured update of the worldwide safety experience for a registered medicinal product, prepared for submission to regulatory authorities at defined times post authorization”. The contents of a PSUR are as follows:

1. Introduction
2. Worldwide market authorization status

3. Update of regulatory authority or Marketing Authorization Holder (MAH)↔actions taken for safety reasons
4. Changes to reference safety information
5. Patient exposure data(Marketed Use, clinical trials ,post marketing studies)
6. Presentation of Individual case histories.
7. Studies
8. Other Information
9. Overall Safety Evaluation(R/B Analysis)
10. Conclusions
11. Appendices

The periodicity and contents as required in US and EU can be summarized as follows:

1. Even if not marketed
2. Six-monthly- first 2 years
3. Annual –subsequent 2 years
4. At the first renewal , and then
5. 5-yearly at renewal thereafter
6. Based on IBD
7. One PSUR for each active substance
8. To be submitted within 60 days of last data lock

US Requirements:

1. Pre- approval PSUR-4months after application
2. Post –approval for each approved NDA/ANDA/BLA
3. Quarterly- for first 3 years
4. Then annual interval / on request
5. Within 30 days of the close of Quarter
6. Annual reports within 60 days
7. Divided into 4 sections
8. Section – 1:15 day alert reports
9. Actions taken(labeling changes/ new studies)
10. Line listing of reporting form (other than above)
11. FDA forma 3500A

CLINICAL TRIALS AND PHARMACOVIGILANCE : INDIAN SCENARIO

Clinical Research is currently in the news for its immense business potential in India. The current 30 million US dollar business is likely to increase tenfold by the year 2010. The only possible hurdle, which could seriously hamper such a development, is the acceptance of such data by the global regulatory authorities, in general and the US FDA, in particular. According to the US FDA Federal Regulation of 1938, establishing the safety of a new molecule is a pre-requisite for obtaining a marketing approval. This was further corroborated by the infamous thalidomide tragedy in 1962, which amply demonstrated that the "Safety" consideration must take precedence over the "Efficacy" consideration of NCE. Ever since, all regulators and healthcare authorities, worldwide have established very stringent codes for conducting clinical trials. These guidelines have undergone constant evolution, starting from Helsinki declaration adopted by the World Medical Assembly (WMA) in 1964 to the current ICH-GCP guidelines. The only aim of these directives is to safeguard the rights and well-being of the trial subjects.

"Efficacy" of a new molecule can be demonstrated through 'positive findings' (results) that indicate its therapeutic usefulness. On the other hand "Safety" of the new molecule can only be established by its 'lack of relative risk' to the patients. This can be done only if the trial subjects on study medications are closely and diligently monitored for 'possible' adverse experiences / reactions during the study. The timely and continuous analysis of the safety and efficacy data in terms of 'Risk/Benefit Ratio' of the NCE is very critical to the conduct of the study involving the new molecule.

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It is important that irrespective of the seriousness, expectedness or causality assessment, all adverse events experienced (and not only ADR's where causality is implied) are monitored, documented adequately & accurately and then reported in a pre-decided timely manner. Medical evaluation of the safety data, alone would ensure safety and well-being of the trial subjects.

Though it is critical to monitor and collect maximum possible information about the patient (Demographic details, medical history), medication and the event itself (temporal relationship, concurrent illness, if any), it's all the more necessary that the Serious Adverse

Events(SAE's) are reported by the investigators to the sponsors in the prescribed format within pre-defined timelines, in an expedited manner. This is essential in order to comply with the strict regulatory requirements all over the world. Often it is necessary to do a follow up of the ongoing Adverse Event (AE), till its resolution and the causality assessment from the investigator is most desirable.

DEFINITION OF PHARMACOVIGILANCE

“This is the science of collecting, monitoring, researching, and evaluating data on the effects of medicinal drugs, biological products, herbals and traditional medicines with a view to identifying new information about adverse reactions and preventing harm to patients”.

Aims of Pharmacovigilance:

The aims of the pharmacovigilance can broadly be described as follows;

- Improve patient care and safety in relation to the use of medicines and all medical and paramedical interventions
- Improve public health and safety in relation to use of medicines
- Contribute to the assessment of benefit, harm, effectiveness, and risk of medicines, encouraging their safe, rational, and more effective use
- Promote understanding, education and clinical training in pharmacovigilance and its effective communication to public.

Adverse Event/ Adverse Experience(AE)

Any untoward and undesirable experience in a patient or clinical investigation subject administered a medicinal product and that dose not necessarily have a casual relationship with this treatment.

The WHO defines an AE as:

“Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which dose not necessarily have a casual relationship with this treatment.”

Adverse Drug Reaction (ADR)

A response to a drug which is noxious and unintended, and which occurs at doses normally used for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiologic function.

To this basic definition, the European Union adds the following:

A reaction, contrary to an event, is characterized by the fact that a casual relationship between the drug and the occurrence is suspected, i.e. judged possible by the reporting or reviewing healthcare professional.’ ‘ An adverse drug that is judged to be caused by the drug’.

Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect.

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed in the serious adverse event definition occurred. Important medical event that may not be immediately life threatening or results in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious.

A list of “critical terms” compiled by WHO may be used as a guiding document to assess seriousness of such an Adverse Event that may be considered medically important.

CAUSALITY ASSESSMENT

The Food and Drug Administration (FDA) define causality assessment as;

“Determination of whether there is a reasonable possibility that the product is etiologically related to the adverse experience. Causality assessment includes, for example, the assessment of temporal relationships , dechallenge / rechallenge information, association (or

lack of association) with underlying disease, and the presence (or absence) of a more likely cause and physiological / pathological plausibility”.

Causality assessment of AEs is the structured and standardized assessment of individual patients / case reports for the likelihood of involvement of suspected drug in causing particular event in a given patient. Basically , it is an exercise to assess whether there is a reasonable possibility that the adverse events associated with the marketed product or study medication.

For fair medical evaluation of every case, it is important that the reporting physician’s assessment of causal relationship is obtained. In order to medically evaluate the cases for causality, the following criteria can be made use of,

1. Pharmacological plausibility.
2. Temporal relationship between administration of suspect drug and onset of ADR.
3. Response to rechallenge
4. Response to dechallenge or presence of established risk factor.
5. Alternative explanation to ADR.

In assessing causality, the above mentioned criteria can be further elaborated as follows;

1. Timing or temporal relationship (time interval between taking the drug and the appearance of the AE/ADR, i. e plausibility and consistency of time to onset between cases)
2. Dose-response relationship (Positive dose response, known effect in drug overdose cases)
3. Pharmacology (there is a known mechanism, the drug is known to affect the same body system as the AE/ADR , pharmacokinetic evidence , recognized class effect of the drug, similar findings in animal studies, biological / pharmacological plausibility)
4. Withdrawal (positive dechallenge)
5. Reproducibility of event upon re-exposure (positive rechallenge)
6. Pattern / previous cases (evidence from clinical trials and / or post marketing surveillance studies, similar AEs / ADRs already recognized for the drug, clear-cut easily evaluated cases ,high frequency of reports , recognized consequence of drug overdose)
7. Opinion of reporter (reports being of high status(credibility)
8. Absence of alternative causes (lack of confounding factors, lack of obvious alternative explanations , concomitant medication being unlikely to have played a role).

The expression 'reasonable casual relationship' means that there is evidence of reasonable suspected casual relationship to the means that there is evidence of reasonable arguments that might suggest a casual relationship.

In clinical trials , causality assessment is the judgment of either the investigator or the sponsors' safety department. The final decision of the investigator conducting a clinical trial of the causality normally, be changed. Again , the classification given by the doctor should not be overruled by the sponsor. If the MAH /licensed manufacturer disagrees with the causality classification of the investigator , a comment from MAH/ licensed manufacturer should be provided.

DECHALLENGE: The clinical decision for withdraw / discontinue a drug treatment after a possible ADR has occurred. The response to dechallenge is a major factor used in the evaluation of causality assessment. A dechallenge is positive or suggestive if the reaction abates, partially or completely when the drug is withdrawn and is considered to the 'negative' or 'against' if the reaction does not abate when the treatment is stopped. A dechallenge is positive if the event/ reaction appears after each dose and abates after a time. Dechallenge may not be evaluable (eg. Reaction resulted in death) or may be irreversible. It is also not applicable where;

- Drug is one dose treatment(vaccine)
- Reaction occurred after the drug was discontinued
- Lack of efficacy, congenital anomaly.

RECHALLENGE: The deliberate or inadvertent administration of a further doses of the same medicinal product to a person who has previously experienced an adverse event / adverse drug reaction that might be drug related. The Food and Drug administration having caused on adverse experience following a positive dechallenge. Failure of the product, when reintroduced , to produce signs and symptoms similar to those observed when the suspect drug was previously introduced implies a negative rechallenge, while recurrence of similar signs and symptoms upon reintroduction of the suspect product implies a positive one.

The response to rechallenge is a major factor used in the causality assessment of drug causality.

A rechallenge is not applicable if:

- The suspect drug was a one-dose treatment
- The drug was not discontinued and reintroduced
- The event/reaction occurred after the product was discontinued.

For ethical reasons, deliberate rechallenge is rarely performed, but it may be carried out when the results are in the interest of the patient suffering the reaction, particularly when there are no suitable alternative drugs.

There are 2 stages of causality assessment:

1. Causality assessment -1st stage :Assessment of individual case reports.
2. 2nd stage: Interpretation of aggregated data

RESPONSIBILITIES OF STAKE HOLDERS

It is essential that the Sponsors and the Investigators particularly and other stake holders like Ethics Committees and the Regulators diligently heed for their responsibilities, the gist of which is summarized under here:

Responsibilities of the Sponsor:-

- 1) To have proper Standard Operating Procedures (SOPs), which would discuss and ensure
 - Protocol design with respect to safety aspects
 - Process involved and
 - Timelines in safety reporting.
- 2) It is also the responsibility of the Sponsor to train
 - Study team and
 - Investigators in the process of safety reporting.
- 3) To have resources and infrastructures to monitor, document and communicate safety information.
- 4) Compilation and evaluation of safety reports on an ongoing basis to assess benefit/risk.
- 5) Dissemination of information to all concerned parties such as regulators, investigators and ethics committees.

Responsibilities of Investigator:-

- 1) To understand the protocol requirements, particularly in relation to safety reporting.
- 2) To train his team members on safety monitoring, reporting and oversee the safety monitoring.

- 3) To provide necessary resources and infrastructure to monitor, document and communicate safety information (fax, telephone and e-mail).
- 4) To whom it may concern: Monitor, capture and documents all adverse events.
- 5) To report the safety information accurately and legibly in prescribed formats and within the timelines as per the protocol.
- 6) To disseminate safety information to concerned parties, such as ECs and IRBs.
- 7) It is expected of the Investigator and his team:
 - To provide medical care to the subject, in case of an AE.
 - To follow up the AEs till resolution.
 - To whom it may concern: Respond to queries.
 - Archive the records for 15 years.

Responsibilities of Ethics Committees and Regulators:-

The greatest responsibility of the ECs and Health Authorities (Regulators) is “To keep a check on ongoing Clinical Trials to ensure the safety and well-being of the trial subjects”.

This can be done by:

- 1) Evaluating trial documents.
- 2) Evaluating measures outlined in the trial documents regarding patients’ safety.
- 3) Timely reviewing reported adverse events, in particular, the serious adverse events and adverse events of special interests.
- 4) Evaluating benefit/risk of the study on an ongoing basis.
- 5) Initiating appropriate and timely action.

Data and Safety Monitoring Board (DSMB):-

The DSMB is an expert committee, independent from the Investigators and the Sponsor of the trial, which periodically examines the safety data accumulated during progress of the trial and ensures that the benefit/risk ratio remains acceptable for participating patients.

A DSMB will be required for;

- Multicenter trials
- All phase III Clinical Trials

For studies requiring a DSMB, a description for the DSMB must be provided in the Data Safety Monitoring Plan (DSMP). The board should include clinicians, statistician, ethicist,

epidemiologists, scientists from other fields and members from outside the institution not directly affiliated with the study.

NATIONAL AND INTERNATIONAL REGULATORY REPORTING NORMS

Indian Regulatory Requirements as per Schedule Y

According to the amended Schedule Y, the responsibilities of the Sponsors in safety reporting are given in clause 2; which is as follows:

“Any unexpected serious adverse event (SAE) occurring during a Clinical Trial should be communicated promptly (within 14 calendar days) by the Sponsor to the Licensing Authority and to the other Investigator(s) participating in the study”.

Whereas the responsibilities of the Investigator(s) in safety reporting are given in clause 3, which is as follows:

“Investigator(s) shall report all serious and unexpected adverse events to the Sponsor within 24 hours and to the Ethics Committee that accorded approval to the study protocol within 7 working days of their occurrence”.

Appendix XI [Format for ICSR submission to DCGI]

Data elements for reporting serious adverse events occurring in a Clinical Trial are as follows:

- 1) Patient Details (Identifiers)- Mandatory
 - Initials and other relevant identifier (hospital/OPD record number etc.)
 - Gender
 - Age and/or date of birth
 - Weight/height.

2) Suspected Drug(s)- Mandatory

- Generic name of the drug
- Indication(s) for which suspect drug was prescribed or tested
- Dosage form and strength
- Daily dose and regimen (specify units- e.g., mg, ml, mg/kg)
- Route of administration
- Starting date and time of the day
- Stopping date and time, or duration of treatment
- Other treatment(s)

Provide the same information for concomitant drugs (including non-prescription/OTC drugs) and non-drug therapies.

3) Details of Adverse Drug Reaction(s)

- Full description of reaction(s) including body site and severity, as well as the criteria for regarding the report as serious. In addition to a description of the reported signs and symptoms, whenever possible
- Describe a specific diagnosis for the reaction- Mandatory
- Start date (and time) of onset of reaction
- Stop date (and time) or duration of reaction
- Dechallenge and rechallenge information
- Setting (e.g., hospital, out-patient clinic, home, nursing home)

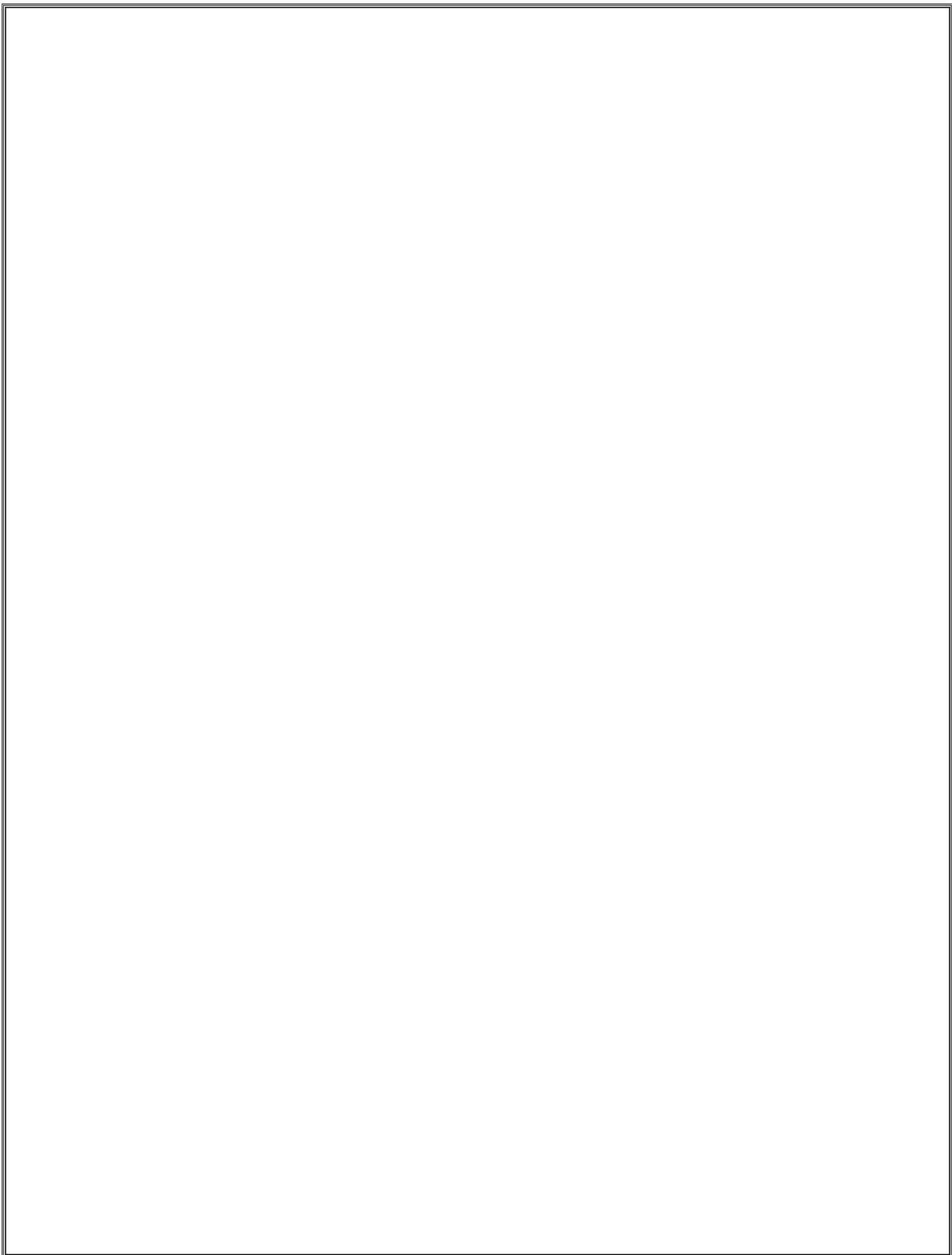
4) Outcome

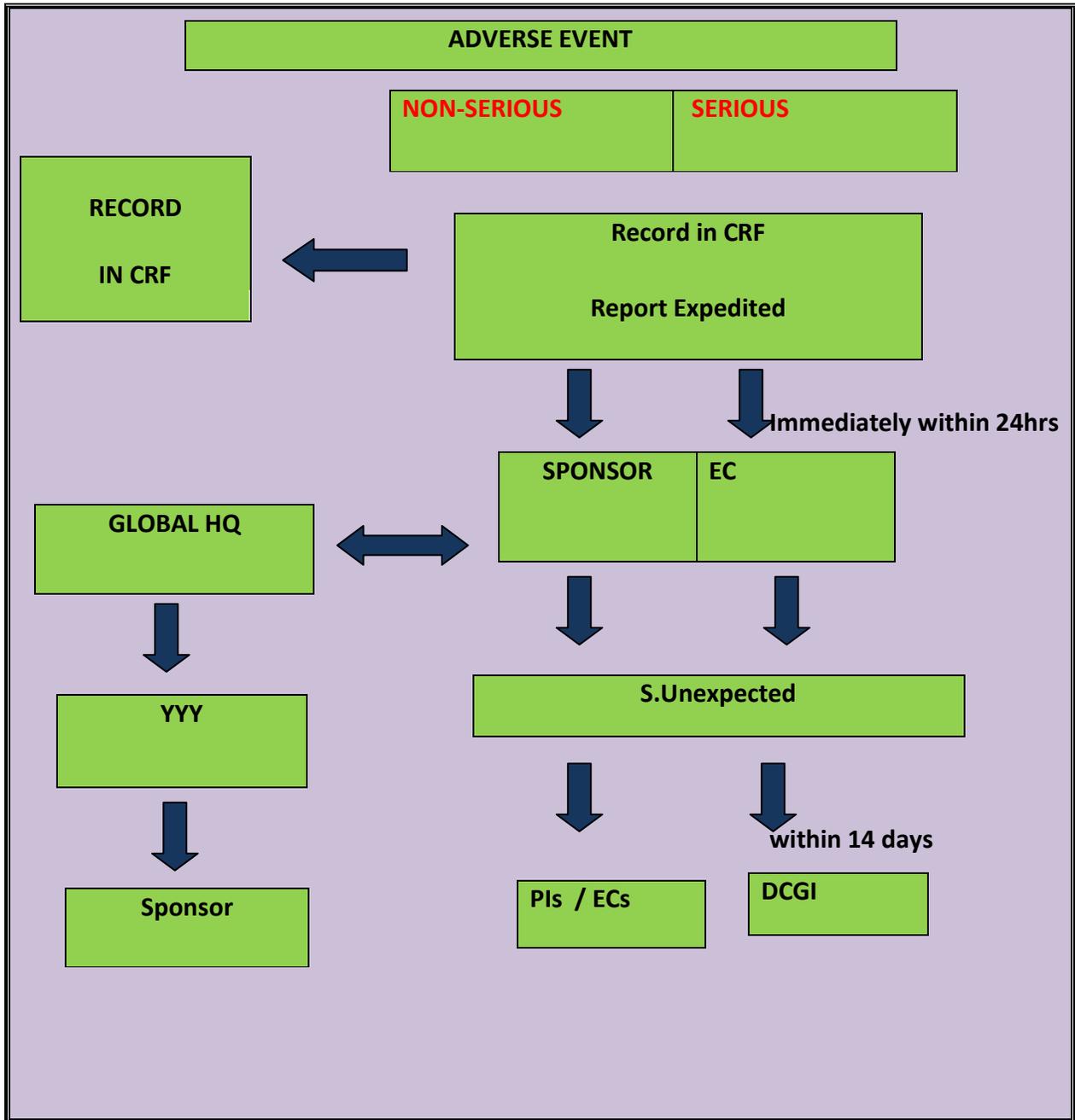
Information on recovery and any sequelae; results of specific tests/treatment that may have been conducted. For fatal outcome, cause of death and a comment on its possible relationship to the suspected reaction; any postmortem findings.

Other information: medical history including allergy, drug or alcohol abuse; family history; findings from special investigations, etc.

5) Details about the Investigator- Mandatory

- Name and address/telephone number
- Profession (specialty)
- Date of reporting the event to Licensing Authority
- Date of reporting the event to Ethics Committee overseeing the site
- Signature of the Investigator





INTERNATIONAL REPORTING REQUIREMENTS

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Expedited single case reports from clinical trials are accepted by majority of the Regulatory Authorities (RAs) on the CIOMS I or similar forms. With the adoption of ICH Guidelines, which define standard data elements for electronic submission, some RAs have begun to require the electronic submission of expedited reports in the post-marketing scenario. More recently, the European Union and Japan have begun requiring electronic submission of the expedited reports from CTs as well. While the time frame and reporting criteria for expedited reporting are mostly consistent across the regions, there are authorities which, require expedited reporting of suspected SADR, regardless of 'expectedness'.

The CIOMS VI Working Group endorses the ICH Guidelines for expedited reporting and recommends that ,”Under exceptional circumstances and on an ad hoc basis , should sponsor be expected to report on an expedited basis SADR that are considered expected”.

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PROCESSES AND PROCEDURES

TIPS FOR SAFETY MONITORING AND REPORTING DURING CLINICAL TRIALS

In order to monitor, document, disseminate and evaluate safety information (issues) in clinical trials, a simple checklist is as follows:

1. Prepare SOP, encompassing the entire process of safety during the trial.
2. Design the SAE reporting form
3. Have necessary infrastructure in place, which should include the following equipments, but not limited to;
 - Multi-connection telephone ,cell phone
 - Computer(database, word processor)
 - Printer (computer linked)
 - Fax

- E-mail

4. Include safety reporting details in the protocol and monitoring plan
5. Train all the stakeholders, like internal team – members , investigators and his team members.
6. Ensure that the sites have infrastructure necessary for safety monitoring and reporting.
7. Check for adverse events while monitoring.
8. Ensure that all AEs are recorded on the CRFs.
9. Ensure that all SAEs are reported in an expedited manner to the sponsor
10. Create database and documentation system for incoming safety information
11. Investigator to forward all such SAEs to the respective IRB/EC.
12. Sponsor to report all SAEs to global team
13. Report to local regulator , in the prescribed format and timelines all those cases which qualify for such reporting
14. File acknowledgement received from the regulatory authority.
15. Disseminate all such cases submitted to local health authorities to other investigators and ECs.
16. Obtain and file acknowledgements from the ECs.
17. Forward all ‘15 day IND-Safety Alerts’ (SUSARs and DILs) received from global team to all the investigators participating in the study.
18. Obtain acknowledgement from the Investigators /ECs.

Health and Academia

The efforts of clinical pharmacology and pharmacy departments around the world have resulted in development of pharmacovigilance as a clinical discipline. A no. of medical institutions have developed adverse reaction and medication error surveillance systems in their clinics, wards and emergency rooms. Case- control studies and other pharmacoepidemiological methods have increasingly been used to estimate the harm associated with medicines once they have been marketed.

The expansion of scientific knowledge in drug safety is attributable to greater awareness and academic interest in this field. Academic centers of pharmacology and pharmacy have played an important role through teaching , training , research , policy development , clinical research , ethics committees and the clinical services they provide . In many medical institutions, particularly in the developed world, ADR monitoring is recognized as an essential quality assurance activity. The growing alliance between the industry and academia and drug regulatory authorities has implications for pharmacovigilance. These are referred to in

- **Health Professionals:** The success of any spontaneous reporting system depends on the active participation of reporters. Although

limited schemes for reporting by patients have been initiated recently , health professionals have been major providers of case reports of suspected ADRs throughout the history of pharmacovigilance. Originally physicians were the only professionals invited to report as judging whether disease or medicine causes a certain symptom by exercising the skill of differential diagnosis. It was assumed that accepting ADR reports from physicians only, would ensure high quality information and minimize the reporting of unrelated, random associations. Studies have shown, however, that different categories of health professionals will observe different kinds of drug related problems. In order to get a representative picture of reality, all sectors of healthcare system would need to be involved, such as public and private hospitals, general practitioners, nursing homes, retail dispensaries, and clinics for traditional medicine. Wherever medicines are being used there should be a readiness to observe and report unwanted and unexpected medical events.

- **Patients:** Only a patient knows the actual benefit and harm of a medicine taken. Observations and reports made by health professional will be an interpretation of a description originally provided by the patient, together with objective measurements. Patients who suspect they have been affected by an ADR are normally recommended to report it to the pharmacovigilance centre. However, since only 5% of doctors are estimated to participate in any pharmacovigilance system, this process is not efficient in ensuring that the patient's concerns are being recorded. There are studies indicating that systems for recording patients concerns might identify new drug safety signals earlier than the professional reporting systems alone.
- **Post –marketing safety monitoring:** It is now generally accepted that part of the process of evaluating drug safety needs to happen in the post – marketing (approval) phase, if important innovations are not to be lost in an unduly restrictive regulatory net. The stronger the national system of pharmacovigilance and ADR reporting , the more likely it is that reasonable regulatory decisions will be made for the early release of new drugs with the promise of therapeutic advances. Careful safety monitoring is not confined to new drugs or to significant therapeutic advances. It has an important role to play in introduction of generic medicines and in review of the safety profile of older medicines already available, where new safety issues

may have arisen. In a developing country, these latter considerations are likely to be more important than the benefits a novel therapeutic entity might bring to an already pressed health service. While spontaneous reporting remains a cornerstone of pharmacovigilance in the regulatory environment, and is indispensable for signal detection, the need for more active surveillance has also become increasingly clear. Without information on utilization and on the extent of consumption, spontaneous reports do not make it possible to determine the frequency of an ADR attributable to a product, or its safety in relation to a comparator.

There are other aspects of drug safety that should be included in monitoring latent and long-term effects of medicines. These include:

- Detection of drug interactions
- Measuring the environmental burden of medicines used in large populations
- Assessing the contribution of ‘inactive’ ingredients to the safety profile
- Systems for comparing safety profiles of similar medicines
- Surveillance of adverse effects on human health of drug residues in animals, eg: antibodies and hormones.

REGULATORY INSPECTION

Inspections by regulatory authorities is a common practice, and sponsors and investigators should always be in a ‘Audit- Ready’ mode. An audit conducted by a regulatory authority is termed as an ‘Inspection’.“ A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed and accurately reported, according to the protocol, sponsor’s SOP, GCP and the applicable regulatory requirements”.

The inspections can be Clinical Trial related or pharmacovigilance related, as a part of routine regulatory process (e.g. GCP compliance, GMP compliance, new drug approval process) or a targeted ‘for-cause’ (eg. Specific ADRs investigations or Recall related) audit. Hence, there can be specialist inspectors with a given task or inspectors during a routine surveillance activity. It is important to know that inspectors only expect that a company has performed what is reasonable. They cannot expect 100 percent in everything- only the key areas of reporting timelines and administrative adequacy. They would however see that when mistakes occur there are processes in place to enable timely action.

Risks and Crisis Management

The importance of an efficient system for dealing with drug safety risks and crises has become increasingly evident in recent years. Drug safety issues tend rapidly to take on international significance. Many national authorities have identified the need for developing an organizational plan for managing risks and for communication and action during crises. Regulators themselves often react under duress in a drug safety crisis within a legislative or administrative framework that is inadequate or excessively restrictive. There should be clear yet flexible operating procedures so that their response is not delayed, unnecessarily complicated, or unduly cautious . In such circumstances, the greater the disparity in safety information between the pre-registration evaluation and the real situation in practice, the greater is the likelihood that the regulatory response will be inappropriate. When crises arise, the regulatory authority has powers to suspend registration, impose special conditions , or severely restrict use to certain patients or prescribers. The authority may require manufacturers to change the product information in a specified manner. These decisions are normally communicated by drug alerts, general letters to doctors and pharmacists , press statements , through websites , newsletters and journal publications , depending on the type and urgency of the message and those who are being addressed.
