ADVERSE EVENT

REPORTING

By
Asma, Jyothi & Maseera
CONTENTS:

- INTRODUCTION
- DEFINITION
- TYPES OF ADVERSE EVENTS
- PRE-MARKETING APPROVAL OF DRUG
- POST MARKETING SURVEILLANCE
- ADVERSE EVENT REPORTING SYSTEM
- ADR MONITORING AND PHARMACOVIGILANCE ACTIVITIES IN INDIA
- ADVERSE EVENT REPORTING FORMS
- GUIDELINES
  1. INDIAN
  2. U.S
- CONCLUSION
- REFERENCES
INTRODUCTION

"Adverse drug reaction" or an "adverse reaction" means a response to a medicine in the humans or animals, which is noxious and unintended, including lack of efficacy, and which occurs at any dosage and can also result from an overdose, misuse or abuse of a medicine.

Pharmacovigilance is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicines.

Definition:

An Adverse Event (AE) is an unanticipated problem involving “risk” to subjects that ultimately results in harm to the subject (impacts on subject’s morbidity and mortality) or others. AE reports must be filed with the sponsor and the Institutional Review Board (IRB) when any of the following happens to a subject on a study:

1. Death
2. Unanticipated “risk” requiring treatment, hospitalization or prolongation of existing hospital stay
3. Any suspicious findings that may have relationship to the study
4. Adverse pregnancy outcome before, during and at the time of delivery
5. Birth defects or congenital anomaly
6. Loss of research records that contain identifiable information
7. Overdose of drug

8. Unusual frequency or intensity of expected effects described in the informed consent document or trends in one type of AE event toward within a protocol (serious or not)

9. Breach of confidentiality

10. Unanticipated problems involving risks to “others” (Example: A nurse in a research study is inadvertently stuck by a needle containing a chemotherapeutic agent that is teratogenic, mutogenic, etc)

11. Abnormal test results that is critical to evaluate the “risk” or “safety” of subjects

12. Unexpected – any adverse experience that is not identified in nature, severity or frequency in the consent form and is not due to a disease process.

**Types of Adverse Events:**

**Serious:** Any adverse event occurring that results in any of the following outcomes: Death, a life-threatening adverse event, requires inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in the previous outcomes may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
**Life-threatening:** An experience that in the opinion of the Investigator places the subject at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

**Others:** Any adverse experience that does not meet the definition of serious. Non-serious adverse experiences can be classified as:

**Severe:** an experience that requires therapeutic intervention. The experience interrupts usual daily activities. **If hospitalization is required for treatment it becomes a serious adverse event.**

**Moderate:** an experience that is alleviated with simple therapeutic treatments. The experience impacts usual daily activities. Includes laboratory test alterations indicating injury, but without long-term risk.

**Mild:** an experience that is usually transient and requires no special treatment or intervention. The experience does not generally interfere with usual daily activities. Includes transient laboratory test alterations.
PRE-MARKETING APPROVAL OF DRUG:

There are three phases of pre-marketing testing for approval of a drug in clinical trials:

**Phase I** consists of the initial introduction of the drug into humans. These are closely monitored and “designed to determine the metabolism and pharmacologic actions of the drug in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.” Studies in this phase also include those for metabolism, structure-activity relationships, and mechanism of action in humans. Phase I studies are needed to produce information regarding the drug’s pharmacokinetics and pharmacological effects in order to properly design Phase II studies.

**Phase II** is designed to evaluate the effectiveness of the drug regarding the disease or condition it is supposed to affect and also determine any common short-term side effects.

**Phase III** studies are greatly expanded and are intended to discover additional information about a drug’s effectiveness and safety. Phase III studies compile information needed to assess the benefit-risk relationship of the drug to determine proper physician labeling.

After FDA is satisfied with the amount of information received and the evidence presented regarding the drug’s safety and effectiveness, it will approve the drug for marketing. Though these three phases of pre-marketing testing can discover vast amounts of information regarding a drug, inevitably side effects of the drug – both minor and major – will be uncovered
after approval. Due to various safeguards protecting patients in the pre-marketing phases of clinical testing, ADEs are constrained. Patients involved in pre-marketing studies rarely represent the real patients the drug is designed for. Variables like age, sex, past medical history, and drug interactions are not taken into consideration and thus limit the studies’ ability to show ADEs. In addition, pre-marketing studies only produce short-term results not reflecting the real length of time actual patients will use the drug. Pre-market clinical trials only expose a few thousand patients to the new drug, whereas millions will be exposed after approval.

This is where post-marketing studies, sometimes referred to as Phase IV studies, become so important. Phase IV studies can detect ADEs that do not arise in the pre-market studies once the drug comes available to a wide variety of patients. The information found during Phase IV provide the first point at which authorities can analyze potential drug safety issues as they occur in large populations. These studies can be useful in identifying dosage effects, evaluating the drug’s effects in special demographics, as well as discovering new uses for it. These Phase IV studies as they are currently implemented, however, still leave many problems in the ADE arena.


POST MARKETING SURVEILLANCE:

(i) Subsequent to approval of the product, new drugs should be closely monitored for their clinical safety once they are marketed. The applicants shall furnish Periodic Safety Update Reports (PSURs) in order to-

(a) Report all the relevant new information from appropriate sources;

(b) Relate these data to patient exposure;
(c) Summarize the market authorization status in different countries and any significant variations related to safety; and

(d) Indicate whether changes should be made to product information in order to optimize the use of the product.

(ii) Ordinarily all dosage forms and formulations as well as indications for new drugs should be covered in one PSUR. Within the single PSUR separate presentations of data for different dosage forms, indications or separate population need to be given.

(iii) All relevant clinical and non-clinical safety data should cover only the period of the report (interval data). The PSURs shall be submitted every six months for the first two years after approval of the drug is granted to the applicant. For subsequent two years – the PSURs need to be submitted annually. Licensing authority may extend the total duration of submission of PSURs if it is considered necessary in the interest of public health. PSURs due for a period must be submitted within 30 calendar days of the last day of the reporting period. However, all cases involving serious unexpected adverse reactions must be reported to the licensing authority within 15 days of initial receipt of the information by the applicant. If marketing of the new drug is delayed by the applicant after obtaining approval to market, such data will have to be provided on the deferred basis beginning from the time the new drug is marketed.

(iv) New studies specifically planned or conducted to examine a safety issue should be described in the PSURs.

(v) A PSUR should be structured as follows:
ADVERSE EVENT REPORTING SYSTEM:

Any ADR system rests on three pillars:

- Collecting new information from reliable scientific resources such as marketing authorization holders, healthcare professionals, consumers, international/public bodies, journals, published and updated literature, etc.
• Classifying and analyzing the above information.

• Circulating its contents as well as any action taken on specific drug to all health sectors. (figure: 1)

**Figure 1: ADR monitoring system**

Four Elements of ADR Reporting

Any ADR report should have the following four main elements:

- Patient
- A drug
- An adverse reaction
- Composer/reporter of the report
## ADVERSE EVENT (EXPERIENCE) REPORTING TIME FRAMES

<table>
<thead>
<tr>
<th></th>
<th>DSMB/Sponsor</th>
<th>CHRMC IRB</th>
<th>FDA</th>
<th>PCRC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>I. RELATED, UNEXPECTED</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Fatal or Life-Threatening | Telephone/FAX within 24 hours  
Written notification within 3 working days of telephone report | Written notification within 3 calendar days  
Follow up reports as soon as information becomes available | Telephone or fax within 7 calendar days  
Written notification within 15 calendar days using FDA form 3500A | Written notification within 7 calendar days  
Follow up reports as soon as information becomes available |
| Serious          | Written notification within 7 calendar days | Written notification within 15 calendar days. | Written notification within 15 calendar days using FDA form 3500A | Written notification within 15 calendar days |
| Severe           | Written notification within 15 calendar days | Written notification within 15 calendar days | Annual report                                 | Written notification within 15 calendar days |
| Mild/moderate    | As per protocol                      | Quarterly                                      | Annual report                                 | Annual report                             |
| **II. RELATED, EXPECTED** |                                     |                                                 |                                                |                                           |
| Fatal, Life-Threatening | Written notification within 7 days | IRB status report                              | Annual Report                                 | Annual report                             |
| Serious          | As per protocol                      | IRB status report                              | Annual Report                                 | Annual Report                             |
| Severe           | As per protocol                      | IRB status report                              | Annual report                                 | Annual report                             |
| Mild/moderate    | As per protocol                      | IRB status report                              | Annual Report                                 | Annual Report                             |
| **II. NOT-RELATED** |                                     |                                                 |                                                |                                           |
| Fatal, Life-Threatening | Written notification within 10 days | IRB status report                              | Annual Report                                 | Annual Report                             |
ADR MONITORING AND PHARMACOVIGILANCE ACTIVITIES IN INDIA:

The National Pharmacovigilance Advisory Committee (NPAC) monitors the performance of various zonal, regional, and peripheral centers and performs the functions of "Review Committee" for this program. The NPAC also recommends possible regulatory measures based on pharmacovigilance data received from various centers. The Zonal Pharmacovigilance Centre (ZPC) and Regional Pharmacovigilance Centre (RPC) have also been established. The Central Drugs Standard Control Organization (CDSCO) is initiating a countrywide pharmacovigilance program under the Family Welfare, and Government of India. The National Pharmacovigilance Centre at CDSCO shall coordinate the program. The National Centre will operate under the supervision of the NPAC to recommend procedures and guidelines for regulatory interventions. The National Pharmacovigilance Program will have the following milestones:

- Short-term objectives: To foster a culture of notification.
- Medium-term objectives: To engage several healthcare professionals and Non-Government Organizations (NGOs) in the drug monitoring and information dissemination processes.
- Long-term objectives: To achieve such operational efficiencies that would make Indian National Pharmacovigilance Program a benchmark for global drug monitoring endeavors.

Periodic Safety Update Reports shall be expected to be submitted every 6 monthly for the first 2 years of marketing in India, and annually for the subsequent 2 years. In addition, training programs and interaction meetings shall be held every 6 months after the initial training [Figure - 2]. Figure - 2. Hierarchical structure of the proposed centers in India
All data generated (including reporting forms) will be stored and preserved for the purpose of archiving for a minimum period of 5 years at the ZPCs. The reporting of seemingly insignificant or common adverse reactions would be important because it may highlight a widespread prescribing problem.

**Information Dissemination**

As has been discussed before, an important task of ADR monitoring and pharmacovigilance planning is to collect new information from reliable scientific resources such as marketing authorization holders, healthcare professionals, consumers, international/public bodies, journals, published and updated literature, etc. followed by classifying and analyzing this information and last but not the least circulating its contents as well as any action taken on specific drug to all health sectors. It is this last provision, which provides important impetus to healthcare professionals and general public.
**ADVERSE EVENT REPORTING FORMS**

Gene Transfer Adverse Event Reporting Template  
Version 4.29.05

<table>
<thead>
<tr>
<th>PROTOCOL AND EVENT TYPE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NIH/OBA (RAC) Protocol Number</strong></td>
</tr>
<tr>
<td>FDA IND number</td>
</tr>
<tr>
<td>Date this report completed:</td>
</tr>
</tbody>
</table>
| **Seriousness of the AE (choose one)** | Death  
Life-threatening  
Initial or prolonged hospitalization  
Disability  
Congenital anomaly  
Required intervention to prevent permanent impairment/damage  
Other medically important condition  
Non-serious |
| **Severity of Event** | Minimal  
Moderate  
Severe  
Life-Threatening  
Fatal |
| **Was this event expected in terms of its severity?** | Yes  
No |
| **Was this event expected in terms of its specificity?** | Yes  
No |
| **Relationship of Event to gene transfer product** | Unrelated  
Unlikely  
Possible  
Probable  
Definite |
| **Attribution of AE** |
| **Attribution of AE, continued** | Concomitant medication  
Product  
Intervention  
Underlying disease  
Route of administration  
Other suspected cause (describe) |
| **Type of report** | Initial  
Follow-up |

<table>
<thead>
<tr>
<th>DEMOGRAPHICS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PI Name</strong></td>
</tr>
<tr>
<td><strong>Name of Clinical Trial Site/Organization</strong></td>
</tr>
<tr>
<td><strong>PI Telephone Number</strong></td>
</tr>
<tr>
<td><strong>PI E-mail Address</strong></td>
</tr>
<tr>
<td><strong>Reporter name</strong></td>
</tr>
<tr>
<td><strong>Reporter Telephone number</strong></td>
</tr>
<tr>
<td><strong>Report E-mail address</strong></td>
</tr>
<tr>
<td>--------------------------</td>
</tr>
<tr>
<td><strong>Research Participant’s study identification number</strong></td>
</tr>
<tr>
<td>Research Participant’s gender</td>
</tr>
<tr>
<td>Research Participant’s date of birth</td>
</tr>
<tr>
<td>Research Participant’s date of death</td>
</tr>
<tr>
<td>Research Participant’s weight in kgs</td>
</tr>
<tr>
<td>Research Participant’s height in cms</td>
</tr>
<tr>
<td>Which Arm/Cohort/treatment group was the subject assigned to?</td>
</tr>
<tr>
<td>Was subject dosed?</td>
</tr>
<tr>
<td>What study agent was received:</td>
</tr>
<tr>
<td>Were there any Protocol Deviations/Violations/Exceptions for this participant?</td>
</tr>
</tbody>
</table>

**DETAILED ADVERSE EVENT INFORMATION**

**Adverse Event Date**

<table>
<thead>
<tr>
<th><strong>Description of Event</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant tests (e.g. x-rays) and results</td>
</tr>
<tr>
<td>Treatment (s) of Adverse Event (Include medications used to treat this event.)</td>
</tr>
<tr>
<td>Name of Concomitant Medications (Do not include medications used to treat this event.)</td>
</tr>
<tr>
<td>Pre-existing conditions/ relevant clinical history (if this is an oncology trial, please designate primary disease, e.g. ovarian cancer)</td>
</tr>
<tr>
<td>Date(s) of treatment(s) of the adverse event</td>
</tr>
<tr>
<td>Was autopsy performed?</td>
</tr>
<tr>
<td>------------------------</td>
</tr>
<tr>
<td>Date of autopsy</td>
</tr>
</tbody>
</table>
| Outcome of the event | Recovered/resolved  
Recovering/resolving  
Not recovered/not resolved  
Recovered/resolved with sequelae  
Fatal  
Unknown |
| Documentation accompanying the report  
(e.g., H& P, Progress Notes, Discharge Summary, Lab or Autopsy Reports, Other, etc.) |
| Description of any “other” documentation |

**PRODUCT AND DOSING INFORMATION**

Name of gene transfer product

Vector type (e.g. adenovirus)

Vector sub-type (e.g. type 5, also include relevant deletions)

Lot number

Was the agent manufactured at an NGVL?

Route of administration

Site of administration

Did subject receive the dose specified in the protocol?

If not, what dose was given?

Date of first exposure to study agent?

Date of most recent exposure to study agent?

Total dose received prior to this event?

Total dose quantity administered to subject to date

Unit of measure for a single dose

Dose quantity in a single administration

If courses used, how many were given prior to this event?

How many doses on the last course were given?
This template is intended to facilitate the reporting of adverse events in human gene transfer trials. Completed reports may be sent to NIH Office of Biotechnology Activities, 6705 Rockledge Drive, Suite 750

Bethesda, Maryland
ADVICE ABOUT REPORTING

- Report adverse experiences with medications
- Report Serious adverse events. An event 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 event
  - you don’t have all the details although point nos. 1, 5, 8, 11, 20 & 22 (see reverse) are essentially required.

- Who can report:
  - any health care professional (Doctors including Dentists, Nurses, and Pharmacists),

- Where to report:
  - after completing, please return this form to the same Pharmacovigilance Centre from where you received,
  - a list of country vide Pharmacovigilance Centres is available at www.cdsco.nic.in,
  - in any case of doubt, you may send this form to the National Pharmacovigilance Centre at: Central Drugs Standard Control Organisation, Directorate General of Health Services, Ministry of Health & Family Welfare, Nirman Bhawan, New Delhi 110 011.

- What happens to the submitted information submitted:
  - the information provided in this form is handled in strict confidence. Peripheral Pharmacovigilance will forward this form to the Regional Pharmacovigilance Centres, where the causality analysis is carried out and the information is forwarded to the Zonal Pharmacovigilance Centres. Finally the data is statistically analysed and forwarded to the global Pharmacovigilance Database managed by WHO Uppsala Monitoring Center in Sweden.
  - the data is periodically reviewed by the National Pharmacovigilance Advisory Committee constituted by the Ministry of Health and Family Welfare, The Committee is entrusted with responsibility to review the data and suggest any interventions that may be required.

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Adverse Drug Event Reporting Form

For VOLUNTARY reporting of adverse drug events by health care professionals

Central Drugs Standard Control Organisation
Directorate General of Health Services,
Ministry of Health & Family Welfare, Government of India,
Nirman Bhawan, New Delhi 110011
www.cdsco.nic.in

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ATTENTION
HEALTH CARE PROFESSIONALS

Your 5 Minutes Can Help Us Ensure Safer Medications
The above form is Adverse event reporting form CDSCO
INDIAN GUIDELINES:

In the Drugs and Cosmetics Rules, 2005 (hereinafter referred to as said rules), (1) in Part X-A, after rule 122-DA, the following shall be inserted, namely:-

122-DAA, Definition of Clinical trial.- For the purpose of this Part, “Clinical trial” means a systematic study of new drug(s) in human subject(s) to generate data for discovering and/or verifying the clinical, pharmacological (including pharmacodynamic and pharmacokinetic) and/or adverse effects with the objective of determining safety and / or efficacy of the new drug.”

With the latest amendment (dated 20th Jan 2005) to the Schedule Y of Drugs and Cosmetic Act 1945, the reporting of adverse events from clinical trials has become clearer and unambiguous. There is of course a quantum leap between the old and the new version and the serious intentions of the Drug Controller General of India (DCGI) regarding stricter compliance are clearly palpable.

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

Any unexpected serious adverse event (SAE) (as defined in GCP Guidelines) 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) safety reporting are given in clause 3, which are 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”.

The differences between both the versions, w.r.t sponsors’ reporting obligations are summarized in the following:

**New Schedule Y**: All ‘unexpected SAEs’ within 14 calendar days would be communicated to the local regulatory authority & other participating investigators”.

**Old Schedule Y**: “Any unusual, unexpected or serious adverse reaction to be communicated promptly to the local regulatory authority”.

**U.S GUIDELINES:**

FDA regulates clinical studies authorized under sections 505(i) (drugs and biologics) and 520(g)I (devices) of the Federal Food, Drug, and Cosmetic Act. All such clinical studies must be reviewed and approved by an IRE3 before the study is initiated, in a manner consistent with the requirements of 21 CFR part 50 (Protection of Human Subjects), part 56 (Institutional Review Boards), and either part 312 (Investigational New Drug Application) or part 812 (Investigational Device Exemptions). After the initial review and approval of a clinical study, an IRB must conduct continuing review of the study at intervals appropriate to the degree of risk presented by the study, but at least annually. The primary purpose of both initial and continuing review of the
study is "to assure the protection of the rights and welfare of the human subjects". To fulfill the IRE3's obligations to assure the protection of the rights and welfare of human subjects during the conduct of a clinical study, an IRE3 must have information concerning unanticipated problems in the study and changes in the research activity. Such information may be important to the IRE3's review.

Clinical Investigations of Drugs and Biological Products under Investigational New Drug (IND) Regulations

Investigators and sponsors have the following regulatory obligations during the conduct of a clinical investigation:

Investigators are required to report promptly to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is "alarming," the investigation must report the adverse effect immediately.

Investigators are required to report promptly to the IRE3 all unanticipated problems involving risks to human subjects or others. A critical question, however, is precisely which occurrences represent such an unanticipated problem. Sponsors are required to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use".

Sponsors are specifically required to notify all participating investigators, in a written investigational new drug (IND) safety report, of "any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects". Sponsors are further required to identify in
these IND safety reports, all previous safety reports concerning similar adverse experiences and to *analyze the significance of the current adverse experience* in light of the previous reports.

**CONCLUSION:**

To ensure accurate adverse events reporting in clinical trials, there are many issues of concern, they are clear, working definition of adverse events, which takes into consideration severity of AE, whether the AE was expected, and the relationship of the AE to the trial intervention. Because the symptoms of individual adverse events may be subjective, particularly with clinical events, the use of standardized definitions is important. If consensus methods or definitions exist in a given field, it is prudent to use them. Consider what method of adverse event reporting (active vs. passive) is feasible in your studies. The detection of adverse events includes- an adequate amount of study participants, and if possible, includes participants that are similar to the population that you would like to generalize to. In detecting rare events, it is important to allow as much follow-up time on participants as is feasible. In the analysis stage, consider what form of analysis (intention-to-treat or otherwise) might be best for analyzing adverse events in non-adherent participants, and how the reporting method might influence the results. Finally, one should be aware of the systemic issues involved in IRB monitoring of adverse events. Consider using a data monitoring committee (this is now required for most U.S. multi-center trials), and make sure that adequate communication exists between the DMC, IRB, and study investigators.
REFERENCES:

1. Status of adverse drug reaction monitoring and pharmacovigilance in selected countries

2. Pharmacovigilance obligations of the pharmaceutical companies in India, Deepa Arora,

3. Clinical trials and safety reporting under Schedule Y, Dr Moin Don, pharmabiz.com,
   Wednesday, September 28, 2005

4. FDA post-market drug surveillance, Katie Zingg, FOOD & DRUG LAW, Professor Neal
   Fortin, December 7, 2007

5. The Food and Drug Administration (FDA) By Meredith A. Hickmann, Nova Science
   Publication, 2003

6. FDA regulatory affairs, Douglas J. Pisano, David Mantus, CRC Press, 2004

7. Clinical trials: a practical guide to design, analysis, and reporting By Duolao Wang,
   Ameet Bakhai, Remedica 2006