Drug and Therapeutics Committee
Training Course

Session 4.
Assessing and
Managing Medicine Safety

Participants’ Guide
This document was made possible through support provided by the U.S. Agency for International Development, under the terms of cooperative agreement number HRN-A-00-00-00016-00. The opinions expressed herein are those of the author(s) and do not necessarily reflect the views of the U.S. Agency for International Development.

About RPM Plus

RPM Plus works in more than 20 developing and transitional countries to provide technical assistance to strengthen pharmaceutical and health commodity management systems. The program offers technical guidance and assists in strategy development and program implementation both in improving the availability of health commodities—pharmaceuticals, vaccines, supplies, and basic medical equipment—of assured quality for maternal and child health, HIV/AIDS, infectious diseases, and family planning, and in promoting the appropriate use of health commodities in the public and private sectors.

Recommended Citation

The materials may be freely abstracted, quoted and translated in part or in whole by non-profit or educational organizations (for reference or teaching only) provided the original source is acknowledged. They should not be sold nor used for any other commercial purpose.


Rational Pharmaceutical Management Plus
Center for Pharmaceutical Management
Management Sciences for Health
4301 North Fairfax Drive
Arlington, VA 22203 USA
Phone: 703.524.6575
Fax: 703.524.7898
E-mail: rpmplus@msh.org
Web: www.msh.org/rpmplus

Developed in Collaboration with the
World Health Organization
Geneva, Switzerland
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>adverse drug reaction</td>
</tr>
<tr>
<td>DOB</td>
<td>date of birth</td>
</tr>
<tr>
<td>DPT</td>
<td>diphtheria, pertussis, tetanus</td>
</tr>
<tr>
<td>DTC</td>
<td>Drug and Therapeutics Committee</td>
</tr>
<tr>
<td>HMO</td>
<td>health maintenance organization</td>
</tr>
<tr>
<td>IM</td>
<td>intramuscular</td>
</tr>
<tr>
<td>IV</td>
<td>intravenous</td>
</tr>
<tr>
<td>NDA</td>
<td>national drug authority</td>
</tr>
<tr>
<td>RCT</td>
<td>randomized control trials</td>
</tr>
<tr>
<td>USD</td>
<td>U.S. dollar</td>
</tr>
<tr>
<td>VA</td>
<td>visual aid</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
</tbody>
</table>
## CONTENTS

Session 4. Assessing And Managing Medicine Safety ................................................................. 1

<table>
<thead>
<tr>
<th>Purpose and Content</th>
<th>1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objectives</td>
<td>1</td>
</tr>
<tr>
<td>Further Reading</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Key Definitions</th>
<th>2</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Introduction</th>
<th>3</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Adverse Drug Reactions</th>
<th>3</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Premarketing Safety Evaluations</th>
<th>6</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Postmarketing Surveillance of ADRs</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spontaneous Reports</td>
<td>7</td>
</tr>
<tr>
<td>Clinical Studies</td>
<td>7</td>
</tr>
<tr>
<td>Published Case Reports</td>
<td>8</td>
</tr>
<tr>
<td>Meta-Analysis of Clinical Studies</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Corrective Action Concerning Newly Identified ADRs</th>
<th>8</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Determining Causality of an ADR</th>
<th>9</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Causality Assessment of Suspected Adverse Reactions</th>
<th>10</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Implications for the DTC</th>
<th>11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monitoring of ADRs by the DTC</td>
<td>11</td>
</tr>
<tr>
<td>Managing ADRs from Hospitals and Clinics</td>
<td>11</td>
</tr>
<tr>
<td>Prevention of ADRs and Adverse Drug Events</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Adverse Drug Events</th>
<th>15</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Prevention of Medication Errors</th>
<th>17</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Activity 1. Penicillin Anaphylaxis Reported</th>
<th>19</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Activity 2. Acute Respiratory Infection in a Two-Year-Old Patient</th>
<th>20</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Activity 3. Serious ADRs with Phen-Fen Combination Medicine</th>
<th>20</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Summary</th>
<th>21</th>
</tr>
</thead>
</table>
Annex 1. Adverse Drug Reaction Reporting Form ................................................................. 22
Severity Assessment Guide.................................................................................................. 23
SESSION 4. ASSESSING AND MANAGING MEDICINE SAFETY

Purpose and Content

Session 4 provides participants with basic information about assessing and managing medicine safety issues.

Objectives

After attending this session, participants will be able to—

- Describe the significance of adverse drugs reactions (ADRs)
- Describe the significance of medication and prescribing errors
- Understand the principles of medicine safety evaluation
- Understand the management of spontaneous case reports of ADRs and medication errors
- Understand the process of monitoring, evaluating, and preventing ADRs and adverse drug events.

Preparation and Materials

Read the Participants’ Guide.

Further Reading


### Key Definitions

**Adverse drug reaction (ADR)**—The World Health Organization defines an ADR as “any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.”

In other words, an ADR is harm directly caused by the medicine at normal doses, during normal use. An unexpected ADR refers to a reaction, the nature or severity of which is not consistent with domestic labeling or market authorization, or is unexpected from characteristics of the medicine. The term *adverse drug effect* is interchangeable with *adverse drug reaction*.

**Side Effect**—Any unintended effect of a pharmaceutical product occurring at doses normally used in humans which is related to the pharmacological properties of the medicine. Such effect may be either positive or negative. Such effects may be well-known and even expected and may require little or no change in patient management.

**Serious Adverse Effect**—Any untoward medical occurrence that at any dose results in death, requires hospital admission or prolongation of existing hospital stay, results in persistent or significant disability or incapacity, or is life threatening.

**Adverse Drug Event**—Any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment, that is, an adverse outcome that occurs while the patient is taking the medicine but is not, or not necessarily, attributable to it.

**Causality**—The probability that a particular medicine or substance is responsible for an isolated effect or ADR.

**Signal**—Reported information on a possible causal relationship between an adverse event and a medicine, the relationship being previously unknown or incompletely documented. Usually more than one signal report is required to generate a signal, depending on the seriousness of the event and the quality of the information.

**Prescribing error**—Incorrect medicine ordering by a prescriber.

**Medication error**—Administration of a medicine or dose that differs from the written order.

**Negligence**—Medical decision making or care below accepted standards of practice.

---

Introduction

Medicines have become one of the most essential components of health care systems worldwide. Medicines save lives. This indisputable fact makes rational selection, procurement, distribution, and rational use of medicines of paramount importance in health care.

Unfortunately, there are often shortcomings in prescribing and taking medicines. One important concern is that of safety. Medicines are produced synthetically or from natural substances, and most will exhibit some form of side effect or adverse reaction. These side effects or adverse reactions may range from relatively mild to, in rare cases, serious and life threatening. Session 4 discusses medicine safety issues, how to assess the true extent of the problem, and how to monitor and prevent medicine-related safety problems.

Adverse Drug Reactions

ADRs are unexpected, unintended, undesirable, or excessive responses to a medicine, and they may be harmful to the patient. By contrast, side effects are known reactions to a medicine and are typically listed in the medicine’s labeling.

The American Society of Health-System Pharmacists\(^2\) provides another definition of ADR. It describes an ADR as any unexpected, unintended, undesirable, or excessive response to a medicine that—

- Requires discontinuing the medicine (therapeutic or diagnostic)
- Requires changing the pharmaceutical therapy
- Requires modifying the dose (except for minor dosage adjustments)
- Necessitates admission to a hospital
- Prolongs the patient’s stay in a health care facility
- Necessitates supportive treatment
- Significantly complicates diagnosis
- Negatively affects prognosis
- Results in temporary or permanent harm or disability, or in death

ADRs can be classified into six types—

- **Type A reactions** (dose-related)—These reactions are an exaggerated, but otherwise normal pharmacological responses to the effects of the medicines given in therapeutic dose, cause significant morbidity but are rarely severe. The reaction is treated by reducing the dose or withholding the medicine and considering alternative therapy.
  - Pharmacodynamic (e.g., bronchospasm from beta-blocker administration)
  - Toxic (e.g., deafness from overdosing of aminoglycosides)

• **Type B reactions** (non-dose related)—These reactions are bizarre and unpredictable with no relation to dose or pharmacological action of the medicine and are often allergic in nature. They are uncommon but are often severe and cause high mortality. The reaction is treated by stopping the medicine and avoiding it in the future. Examples of such reactions include—
  o Medicine-induced diseases (e.g., antibiotic-associated colitis)
  o Allergic reactions (e.g., anaphylactic reaction to penicillin administration)
  o Idiosyncratic reactions (e.g., irreversible aplastic anemia caused by chloramphenicol)

• **Type C reactions** (dose-related and time-related)—These reactions are chronic (long term) and related to cumulative dose. The reaction is treated by reducing the dose or withholding the medicine, which may have to be withheld for a long time. Examples of such a reaction include—
  o Osteoporosis with oral steroids
  o Hypothalamic-pituitary-adrenal axis suppression by corticosteroids

• **Type D reactions** (time related)—These reactions are delayed (i.e., have a lag time) after the use of a drug. They are uncommon but their treatment is often intractable. Examples of such reactions include—
  o Teratogenic effects with anticonvulsants or lisinopril
  o Carcinogenesis
  o Tardive dyskinesia

• **Type E reactions** (withdrawal)—These reactions occur soon after the end of use (i.e., withdrawal) and are uncommon. The reaction is treated by reintroducing the medicine and then withdrawing it slowly. Examples of this reaction include—
  o Withdrawal syndrome with benzodiazepines
  o Opiate withdrawal syndrome
  o Myocardial ischemia after beta-blocker withdrawal

• **Type F reactions** (unexpected failure of efficacy)—These reactions occur when there is a failure of efficacy. Such reactions are common, may be dose-related and are often caused by drug interactions. The reaction is treated by increasing the dose and considering the effects of concomitant therapy. Examples include—
  o Resistance to antimicrobials
  o Inadequate dosage or oral contraceptives, particularly when used with specific enzyme inducers

Adverse reactions as a result of medicine interactions may be manifested in all degrees of severity and type including—

• Reduced absorption of tetracyclines if administered with calcium
• Phenytoin toxicity when administered in conjunction with fluconazole
• Digoxin toxicity when administered with furosemide
ADRs are a serious problem with increasing incidence as more medicines become available and more people become exposed to them. In the United States, a review of prospective studies showed that hospitalized patients in 1994 had 2.2 million ADRs (6.7 percent incidence), which resulted in 106,000 fatalities. These statistics become even more significant considering that they do not include errors of administration, which would only increase the total incidence of morbidity and mortality related to medicine use. The United Kingdom’s National Health Service reports that ADRs resulted in approximately 250,000 admissions each year and cost the health system £466 million (870 million U.S. dollars [USD]) yearly.

Extrapolating these figures to other countries is difficult, but assuming that all countries have a significant problem in terms of ADRs, a subsequent increase in morbidity and mortality as a direct result is reasonable. Most medicines undergo a significant amount of testing and evaluation before marketing to ensure the product is not only effective but also safe. No medicines on the market today are free of side effects or adverse reactions. Many products have an extremely low incidence of side effects, such as cromolyn inhalation products. Others, such as antineoplastic medicines, exhibit extremely high incidence of adverse reactions, many resulting in death. A close monitoring and evaluation of most medicines is necessary to prevent more serious side effects from occurring.

Marketing a new medicine requires many clinical trials to establish efficacy, safety, quality, and cost-benefit. Clinical trials will determine the most common adverse events, those with an occurrence of 1 percent or more during the development of a new medicine. Adverse events that are less common (<1 percent incidence) may not be identified in these premarketing studies and will rely on postmarketing clinical studies and reporting by physicians, pharmacists, and patients for identification of these uncommon events.

Every medicine has a risk-benefit ratio. Depending on the patient’s condition being treated, ancillary problems, age, and many other parameters, the patient can be expected to obtain both a measurable benefit and experience a certain degree of risk. Careful evaluation by the practitioner before use of the medicine is always necessary to obtain the most beneficial effect from the medicine, minimize ADRs, and obtain value for the cost of the product. This evaluation can be accomplished by careful review of the patient’s history, evaluation of current health status, and the avoidance of medicine that may have a higher incidence of ADRs in the patient.

---


Premarketing Safety Evaluations

Premarketing testing is extensive for most medicines that are produced in Japan, North America, and Europe. Typically a new medicine would have the following evaluation before being marketed—

- Animal studies
  - Acute and chronic toxicity—Studies are conducted for various periods, from 14 days to over one year in two or more species of test animal
  - Mutagenicity and carcinogenicity—A battery of mutagenicity tests evaluates the potential for genetic problems; testing is performed in at least two animal species for a period of two years; testing is done only if the medicine is intended for chronic use
  - Teratogenicity—Tests are performed on animal species to assess ability to reproduce and have a normal offspring free of birth defects; the ability of the offspring to grow normally and reproduce is also tested extensively

- Human studies (clinical trials)—Study of the effects of medicines on humans under rigorously controlled trials; most clinical trials will assess safety. The average number of clinical trials performed before a medicine is approved is 68; the average number of patients used in these trials is approximately 4,000.
  - Phase I—Single-dose studies, using low doses of the medicine. Subsequently larger doses and multiple sequences are evaluated.
  - Phase II—Efficacy and safety studies. Efficacy is the primary objective of phase II trials, but safety is also continuously monitored and evaluated.
  - Phase III—Evaluations of safety in groups of patients with the disease. Phase III trials may study the effects of the medicine on, for example, the elderly or patients who have ancillary diseases, use other medicines, and have compromised renal and liver function
  - Phase IV—Postmarketing surveillance and clinical trials

Premarketing safety evaluations have two significant drawbacks—

- Under-identification of ADRs—Low-incidence ADRs, those reactions with an incidence less than 1 percent, are frequently not identified.

- Over-identification of ADRs—Many ADRs that are identified in preclinical studies are not proven to be causal, but are still listed in the product literature as potentially causing the ADR. This practice provides some measure of legal protection for the pharmaceutical
company but is misleading to practitioners, because many of these reactions are not definitely proven.

**Postmarketing Surveillance of ADRs**

After medicines have been released on the market, manufacturers are responsible for postmarketing surveillance of these products. Identifying all of the safety-related problems that may exist with a new medicine is not possible during premarketing testing and evaluation.

Medicines released onto the open market will be used not only by more people, but also by older and sicker people, different ethnic groups, pregnant women, and children and will be prescribed in many different dose regimens (not necessarily the correct and approved dose). These circumstances inevitably lead to a potential for more ADRs.

**Spontaneous Reports**

Spontaneous reports are reports of an ADR by a physician, pharmacist, or patient. In many countries these reports are sent to regulatory agencies or the manufacturer of the medicine.

Spontaneous reports have been shown to identify new ADRs more often than any other method. Consequently, this reporting and identification method has held the most significance for manufacturers over the past 10 years. These reports have the advantage of being available immediately as new products are released and throughout the market life of the medicine. A spontaneous report of a reaction describes the reaction that has occurred, but need only have the suspicion that an adverse event may be related to the use of the medicine. All serious reactions (i.e., those that lead to death, hospitalization, significant or permanent disability, or to congenital abnormality or that require medical or surgical intervention) should be reported. Many less serious reactions should also be reported, especially new and unusual reactions.

The greatest limitation of spontaneous reports is that there is significant underreporting of adverse reactions. Another limitation of spontaneous reporting is a high incidence of false positives in the reporting of adverse events. Many practitioners find accurate assessing and determining the causality of an ADR to be difficult, and the incidence of erroneous reports by physicians and pharmacists is high. Patients are also a source for the reporting of an adverse event and the quality of these reports is frequently unreliable.

Multinational pharmaceutical manufacturers employ a worldwide system of collection, aggregation, and evaluation of ADRs. Data are collected by telephone calls, letters, and literature reviews, and through regulatory authorities. The companies report serious ADRs to regulatory organizations on a regular basis.

**Clinical Studies**

Postmarketing clinical studies are frequently done to assess efficacy and safety. The two methods used are randomized control trials and observational studies.
Randomized Controlled Trials

Randomized controlled trials (RCT) are valuable tools for uncovering adverse events in preclinical studies. For postmarketing discovery of events, however, the RCT is frequently disappointing. The elimination of confounding factors is excellent in this setting, but RCTs generally have insufficient power in the trial to discover an event that was not already observed in premarketing studies. RCTs are also expensive and difficult to manage.

Observational Studies

Large databases from national health programs and from large health maintenance organizations (HMOs) in North America and Europe provide valuable information concerning medicine safety. These databases (with millions of entries) are acceptable for providing information in a case-control or cohort study. A case-control study is a study in which patients who already have a certain condition are compared with people who do not. A cohort study identifies two groups of patients: one that is exposed to the study medicine and another that is not treated or receives an alternate form of therapy.

Pharmaceutical manufacturers frequently set up and sponsor large cohort studies to assess safety issues that have arisen after a medicine has come to market. These studies allow for the control of potential confounders, bias, and chance to a greater extent than spontaneous reports or case reports, but still are susceptible to these factors. Cohort studies are helpful in attempting to assign causality when spontaneous reports indicate a potential for a medicine to cause an adverse event. These types of studies can be unsuccessful because the numbers of patients selected will often be insufficient to provide statistical significance for rare ADRs.

Published Case Reports

Published case reports can be found in medical and pharmaceutical journals and describe the occurrence of a significant ADR. These reports can have drawbacks because they may not be well documented and have a long lead-time from the identification of the event to publication in a journal. These reports are also published at the discretion of editors and publishers.

Meta-Analysis of Clinical Studies

Meta-analysis of published studies is another valuable method to obtain information concerning the incidence and prevalence of ADRs. A meta-analysis takes two or more single studies concerning a particular medicine or reaction and combines them to provide more power for the statistical analysis. Individual reports may not have the statistical power to make conclusions concerning an ADR, but combining several reports will provide the appropriate numbers when one study showed only an insignificant effect.

Corrective Action Concerning Newly Identified ADRs

The surveillance systems currently in place inevitably obtain important new information about medicine safety and ADRs. This information is placed in a database and analyzed by
manufacturers or regulatory agencies. When it becomes apparent that a new safety concern has been detected, appropriate action is taken. The response is usually in one of three forms—

- **Letters**—These letters are sent to physicians and pharmacists describing a concern about a particular medicine. The letter may provide specifics about the new safety concern and how it may affect present patients on the medicine and future prescribing. It may be only a warning of possible safety concerns that have been detected and may recommend a continued vigilance in prescribing and dispensing the medicine.

- **Package insert revisions**—When safety concerns become significant, manufacturers must change the label of the product. This action requires changing the official labeling and changing the package insert to reflect the new safety concern. Regulatory officials typically approve the change.

- **Medicine recalls**—Surveillance systems are intended to monitor medicine safety. Manufacturers and regulatory authorities are responsible for monitoring and assessing the postmarketing surveillance reports. When thresholds for acceptable ADR incidence (or for quality issues) are exceeded and the risk of side effects outweighs the benefits, then withdrawing the medicine from the market may be necessary. Medicine recalls can be voluntary or imposed by regulatory authorities. This action is rarely necessary.

### Determining Causality of an ADR

Causality of an ADR is a critical issue that requires the linking of any adverse event to a medicine or other cause. Manufacturers, drug regulatory agencies, and DTCs must determine causality of isolated ADRs. When a specific symptom occurs following the administration of a medicine, it does not necessarily mean that the medicine is responsible. Numerous other possibilities may be responsible for the adverse event. Conversely, an analyst cannot conclude that, because a particular medicine has not been taken for some time and an adverse event occurs, that the time interval eliminates the medicine as a cause of the event.

The following associations support causation linking a medicine and suspected adverse reaction.\(^5\) (See table 1.)

- Strength of the association
- Consistency of the observed evidence
- Temporality of the relationship
- Dose-response relationship
- Confounding factors

---

Table 1. Determining the Causality of an ADR

<table>
<thead>
<tr>
<th>Association</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strength of association</td>
<td>If the odds are known and high for an observed event (e.g., gastrointestinal upset with aspirin), then the case is strengthened for causation.</td>
</tr>
<tr>
<td>Consistency of the observed</td>
<td>When a medicine and an ADR have an association that has been demonstrated consistently over years of clinical practice, causality becomes more likely.</td>
</tr>
<tr>
<td>evidence</td>
<td></td>
</tr>
<tr>
<td>Temporality of the relationship</td>
<td>The closer the relationship of the administration of the medicine and the occurrence of the ADR, the more likely that the medicine may be the actual cause of the reaction.</td>
</tr>
<tr>
<td></td>
<td>This temporality is not always a true indication, however, because some adverse events may occur several days or weeks after the administration of the offending medicine.</td>
</tr>
<tr>
<td>Dose-response relationship</td>
<td>Frequently, adverse events occur in relation to the dose being administered. The higher the dose of the medicine, the more likely an ADR is a result of the administered agent. A lower dose has a corresponding decrease in the ADR.</td>
</tr>
<tr>
<td></td>
<td>This relationship is not always true, however, because very low doses of some medicines (e.g., penicillin) can elicit serious anaphylactic responses.</td>
</tr>
<tr>
<td>Confounding factors</td>
<td>Minimizing confounding factors is important in determining causality. Confounding factors such as the administration of other medicines, food, and beverages can account for observed events. The existence of concurrent diseases and infections can also cause certain observed effects, so distinguishing them from the suspected medicine is difficult. Environmental factors, such as air pollutants, weather conditions, and exposure to allergens, may also play a role.</td>
</tr>
</tbody>
</table>

Causality Assessment of Suspected Adverse Reactions

The causality categories described in this section were established by the WHO Uppsala Monitoring Centre, Uppsala, Sweden.

Certain causality is when a clinical event (including laboratory test abnormality) occurs in a plausible time relationship to medicine administration and cannot be explained by concurrent disease or other medicines or chemicals. A plausible (expected) clinical response to withdrawal of the medicine must be demonstrated and, if possible, the clinical response to restarting the medicine should also be demonstrated.
Probable or likely causality is when a clinical event occurs with a reasonable time sequence to medicine administration, and it is unlikely to be due to any concurrent disease or other medicine administration.

Possible or likely causality is when a clinical event occurs with a reasonable time sequence to medicine administration, but which could be explained by concurrent disease or other medicine administration. Information on medicine withdrawal may be lacking or unclear.

Unlikely causality is when a clinical event, including laboratory test abnormality, occurs with a temporal relationship to medicine administration that makes a causal relationship improbable, and in which other medicines, chemicals, or underlying disease provide plausible explanations.

Implications for the DTC

Monitoring of ADRs by the DTC

DTCs should implement programs that track and report ADRs throughout the health care system. This effort would include a system for monitoring medicines and vaccines. There are several methods to accomplish this end and at minimum the following would be provided—

- Reporting of ADRs (including vaccines) to the DTC on standard forms (see annex 1)
- Analysis of ADR reports to include statistical analysis of prevalence, severity, and trends in the occurrence of ADRs
- Discussion and evaluation of reports by the DTC on a regular schedule (quarterly) and reporting to medical staff
- Reporting to manufacturers and national regulatory authorities of severe, new, or unusual reactions

Monitoring of ADRs should also include the review of the medication error and product quality reporting systems. These reporting and tracking systems are important because product quality and medication errors may have a significant effect on the occurrence of ADRs.

Managing ADRs from Hospitals and Clinics

The DTC should become involved in the processing and analysis of spontaneous case reports arising from patients and medical providers. These spontaneous reports from practitioners may be difficult to interpret and to assign causality. The following are frequent problems that arise with ADRs reported at a hospital or primary care clinic—

- A particular generic medicine causes an ADR, but the brand name product does not.
- A brand name product is alleged to cause more side effects than another branded product.
• An antibiotic suspension causes a reaction, and it is unclear if responsibility lies with the antibiotic or one of the components of the suspension (i.e., dyes or other excipients in the suspension).

• An injectable product causes a reaction, and it is unclear if the causative agent is the active ingredient or is related to a preservative or other agent in the solvent.

• A patient is on several medicines when a new adverse event is reported; assigning causality becomes problematic because any number of the medicines may be the cause.

• The patient has co-morbid conditions that may have a bearing on the medicine and suspected ADR.

The following steps are necessary to evaluate an ADR observed in the hospital or primary care clinic.

1. Evaluate the nature of the event

   • Obtain a detailed history of the patient including current health status, current pharmaceutical therapy, and past medical history. Use an ADR reporting form to organize reporting. (See annex 1.)

   • Identify and document the clinical reaction. Look up suspected medicines and known ADRs in the literature, and match them with the reactions described by the patient.

   • Classify severity of the reaction—
     - Severe—Fatal or life threatening
     - Moderate—Requires antidote, medical procedure, or hospitalization
     - Mild—Obvious symptoms that require only the discontinuation of pharmaceutical therapy
     - Incidental—Mild symptoms; patient given the option to continue or discontinue medication

2. Establish the cause

   • Use the Naranjo algorithm (or other system) for assessing the reaction and establishing the cause. This algorithm will assist the practitioner in determining the probability that an ADR has actually occurred from the suspected medicine. The algorithm asks a number of questions about the adverse event and provides a numerical rating for the importance of each question. The scores for all items are added to give a probability of causality of the adverse event. (See annex 2.)
• Evaluate the quality of the product from the manufacturer to rule out any adverse event occurring from a poor-quality product. This investigation should include the possibility of pharmaceutical counterfeiting and overt contamination of the product.

• Finally, check for a medication error.

3. *Take corrective and follow-up action*

With information obtained through this process, make a definitive decision based upon the facts as presented. Determine if the reaction is an ADR, adverse drug event (including medication error), or a quality defect. All significant ADRs must be recorded on the patient’s medical record. The following actions may be required of the DTC after the evaluation of serious or recurring ADRs at its hospitals and clinics—

• Educate prescribers.

• Change formulary or standard treatment guidelines, if necessary, to obtain a medicine of proven safety.

• Modify patient monitoring procedures.

• Report to national drug authority and the manufacturer, especially with regard to serious reactions, a new ADR, or an unusual manifestation of a known ADR.

After all ADRs, educate and warn patients to reduce the possibility of ADR recurrence.

*Prevention of ADRs and Adverse Drug Events*

Prevention of many serious ADRs is possible and a necessary function of the DTC. Without a prevention program, many ADRs will occur needlessly, producing an increase in morbidity and associated health care cost. Many authorities agree that over 50 percent of ADRs may be preventable. There is a general lack of knowledge concerning ADRs, including the incidence, severity, and impact on health care. Many ADRs are related to the prescribing of an incorrect dose and to administration of a medicine to a patient with a known allergy. The schematic in figure 1 illustrates the factors that contribute to preventable adverse reactions.
Figure 1. Schematic of preventable and unavoidable adverse events.

Preventing an ADR can be enhanced by the practitioner by evaluating the following before prescribing a medicine—

- Is this medicine the correct one for the patient’s clinical condition?
- Are the dose, route, and interval correct?
- Does the patient have any medical or physical conditions that would affect the pharmacokinetic aspects of the medicine?
- Does the patient have an allergy to this medication or a chemically similar medicine?
- Is the patient on another medicine (or herbal product) that would cause a significant medicine interaction?
- What is the patient’s compliance with the medication?
- Is the medicine being prescribed a medicine that is at high risk for producing ADRs (e.g., aminoglycosides, digoxin, warfarin, heparin, and antineoplastics)? Special precautions are necessary when using these high-risk medicines.
- Is the medicine being prescribed of high quality (i.e., reputable manufacturer, not expired, no deterioration)?
- Is the medicine being administered correctly (e.g., sterile needle or syringe for injectable medicines or with food for gastrointestinal irritants)?
The following actions by the DTC can help limit the occurrence of ADRs—

- Review ADR reports regularly, and inform the professional staff of the incidence and impact of ADRs in the region.
- Discuss changes in the formulary or standard treatment guidelines for significant or recurring problems with ADRs.
- Educate staff, especially providers, concerning ADRs.
  - In-service education
  - Face-to-face education with providers
  - Medicine information bulletins
  - Reports of collected adverse events
- Identify medicines on the formulary that are high risk and should be monitored closely by physicians and pharmacists. For example—
  - Aminoglycosides
  - Antineoplastics
  - Digoxin
  - Heparin
  - Warfarin
- Identify high-risk patient populations, including pregnant women, breast-feeding women, the elderly, children, and patients with renal or liver dysfunction; close monitoring of these patient populations by physicians and pharmacists will help prevent serious adverse reactions.
- Review medication errors and product quality complaints to ensure they are not contributing to the incidence of ADRs at the hospital.

**Adverse Drug Events**

An adverse drug event is any untoward medical occurrence that may be present during treatment with a medicine but does not necessarily have a causal relationship with this treatment. Adverse drug events include medication errors.

Studies of adverse drug events and errors in medication prescribing and administration have been conducted in developed countries where resources for such studies are available. These studies have shown a substantial problem in terms of patient injury and increased cost of health care. The risk of an adverse drug event has been about 1 to 5 percent in U.S. hospitals, and about one-third of the events were preventable. Preventable adverse drug events added more than four days to the length of stay and more than USD 4,000 to the cost of the hospital admission. Most errors that result in adverse drug events occur at the stage of physician ordering or medicine administration.
A record review of 15,000 inpatients in the United States in 1992 revealed that there were 2.9 percent adverse events (30 percent due negligence) and 35 percent adverse drug events due to negligence.\(^6\) Primary medicines involved were—

- Antibiotics—25 percent
- Cardiovascular medicines—17 percent
- Analgesics—9 percent
- Anticoagulants—9 percent

Types of medicine use errors include—

- Wrong medicine prescribed—21 percent
- Prescribed despite known allergy—6 percent
- Incorrect frequency—5 percent
- Wrong dose—8 percent
- Missed dose—5 percent
- Medicine interaction—3 percent

A study of adverse drug events at two major tertiary care hospitals in Boston (Massachusetts General Hospital and Brigham and Women’s Hospital) in 1993 found 247 adverse drug events in 4,031 admissions. Seventy (28 percent) of the adverse events were considered preventable. Overall, the risk of an adverse drug event was about 6.1 percent, and the rate was highest among patients in the medical intensive care unit (19.4 episodes per 1,000 patient days). An analysis was conducted of the 70 adverse drug events due to error and an additional 194 potential adverse drug events due to error (i.e., administration or near-administration of an incorrect medicine without evident harm). The 264 preventable events were attributed to 334 errors. Most errors occurred in the physician ordering (39 percent) and nurse administration (38 percent) stages. The remainder were nearly equally divided between transcription (copying or dictating of medication orders) (12 percent) and pharmacy dispensing (11 percent). Although there were almost as many errors in the administration stage as in ordering, nurses were the ones most likely to intercept errors, especially those made by physicians.\(^7\) On further analysis, the cost of ADEs showed the following—

- 247 adverse drug events were estimated to have—
  - Extended hospitalization by 2.2 days
  - Increased cost of USD 3,244

---

• 70 adverse drug events due to errors were estimated to have—
  o Extended hospitalization by 4.6 days
  o Increased cost of 5,857 U.S. dollars\(^8\)

In a study of pediatric inpatients, 10,778 medication orders were reviewed and 616 contained errors. Of these, 120 (19.5 percent) were classified as potentially harmful, including 115 potential adverse drug events (18.7 percent) and five preventable adverse drug events (0.8 percent). Most errors occurred at the medicine ordering or prescribing stage (74 percent). Transcribing (5.8 percent), dispensing (1 percent), administration (12.8 percent), and monitoring (0.5 percent) accounted for the other reported errors.\(^9\)

The magnitude and causes of the problem of adverse drug events in developing countries are not known. To characterize the problem, it is desirable that individual hospitals establish reporting and monitoring systems. Furthermore, DTCs must take the lead role in developing and disseminating best practice recommendations in each hospital. Important interventions are to provide oversight of physician ordering, especially in intensive care units; to simplify, standardize, and rationalize hospital systems involved in medicine formulation and administration; and to promote adequate staffing so that errors caused by undue haste or fatigue can be avoided.

**Prevention of Medication Errors**

Medication errors are common events in hospitals and primary care clinics. Medication errors consist of the administration of medicine or dose that differs from written order and includes—

• Medicine prescribed but not given
• Administration of a medicine not prescribed
• Medicine given to the wrong patient
• Wrong medicine or IV fluid administered
• Wrong dose or strength given
• Wrong dosage form given
• Medicine given for wrong duration
• Wrong preparation of a dose (e.g., incorrect dilution)
• Incorrect administration technique (e.g., unsterile injection)
• Medicine given to a patient with known allergy
• Wrong route of administration used
• Wrong time or frequency of administration


There are many causes of medication errors but are generally attributed to the following three factors—

- **Human factors**
  - Heavy staff workload and fatigue
  - Inexperience, lack of training, poor handwriting, and oral orders

- **Workplace factors**
  - Poor lighting, noise, interruptions, excessive workload

- **Pharmaceutical factors**
  - Excessive prescribing
  - Confusing medicine nomenclature, packaging, or labeling
  - Increased number or quantity of medicines per patient
  - Frequency and complexity of calculations needed to prescribe, dispense, or administer a medicine
  - Lack of effective policies and procedures

Two broad interventions to reduce medication errors are (a) improve physician prescribing, and (b) correct systems flaws that predispose to errors. Ideally, educational programs for physicians can be developed with a focus on the most common prescribing errors. These errors, however, involve deficiencies in diverse areas, including knowledge of medicine indications and doses, attention to renal and hepatic function, awareness of medicine interactions, and willingness to routinely check allergy history. A more practical alternative has been to assign pharmacists to monitor medication orders written by physicians.

Specific interventions that are practical, at least in tertiary care hospitals, include the following—

- Establish a consensus group of physicians, pharmacists, and nurses to review current medicine prescribing and administration practices and select best practices.

- Introduce a system to identify and record information about medication errors. To encourage reporting, staff should not fear punishment; the focus should be on system redesign rather than blame.

- Where feasible, institute pharmacy-based admixture of IV fluids. If ward personnel must perform IV admixture, there should be clear written procedures and skills certification of the personnel.

- Develop special procedures for high-risk drugs, such as insulin, heparin, narcotics, theophylline, and aminoglycosides. These procedures should include written guidelines, checklists, and educational materials.
• Require legible handwriting by ordering physicians. Pharmacists and nurses should be instructed to call the prescriber rather than try to interpret illegible orders. Require complete spelling of a medicine’s name.

• Use a standardized designation for doses (i.e., milligrams = mg, micrograms = mcg, and grams = g; use the word “units” rather than “U”; and use a leading zero for values less than 1 but not a trailing zero after a decimal, e.g., write 0.2 mg or 2 mg instead of .2 mg or 2.0 mg).

• Write the route of administration on all orders.

• Write out directions completely. Write “daily” instead of “QD” and “every other day” instead of “QOD.”

• Limit the use of oral or telephone orders to emergency situations, and require that the order be read back to the prescriber.

• When preparing to administer a medication, confirm the identity of the patient by reading the patient’s wristband and talking to the patient or family member.

• To minimize the likelihood that a dose will be missed, standardize administration times and develop a policy to provide doses when a patient is off the floor.

• Analyze medicine names as new products are added to the formulary. For look-alike and sound-alike names, establish a policy requiring that prescribers write both brand and generic name.

• Use pharmacy staff effectively to monitor and manage medicine use and distribution.

Activities

For the activities in this session, the participants will break into groups of five or six individuals. A leader will be selected who will facilitate the discussion within the group. Active discussion within the groups is encouraged.

Activity 1. Penicillin Anaphylaxis Reported

A DTC in Panama served 11 clinics and a hospital. Recently a different brand of procaine penicillin had been purchased and distributed. Shortly after introduction of the new penicillin product, one clinic reported to the DTC that they had experienced an unusually high number of adverse events associated with intramuscular penicillin injections within a short period. The nursing staff became alarmed, refused to use the product that had been distributed, and asked the clinic director to replace the suspect product with an equivalent product from another supplier. They described the adverse event as an adult patient suddenly (within seconds of the injection) experiencing feelings of doom, anxiety, and faintness, necessitating lying down. Patients were reported to be pale but with normal or slightly high blood pressure. The nurses immediately gave
the patients diphenhydramine IV or IM for a suspected anaphylactic reaction to penicillin. Patients would recover 10 to 15 minutes later and would leave the clinic without further assistance.

- How would you analyze this situation? What investigations would you carry out?
- What would you recommend to management regarding the procurement of an alternative or equivalent product?
- What would you communicate to the nursing staff and physicians?

Activity 2. Acute Respiratory Infection in a Two-Year-Old Patient

A two-year-old patient and mother present at the clinic on May 19, 1999. The child has a 48-hour history of fever, irritability, cough, and altered consciousness. Questioning of the mother reveals the following—

- 5/14/99—child was administered DPT and oral polio vaccine.
- 5/15/99—child was seen with mild upper respiratory tract infection symptoms and treated with amoxicillin and cough syrup.
- 5/17/99—child experienced the onset of fever, irritability, altered consciousness.
- 5/18/99—child had been seen at the health center and diagnosed with acute respiratory infection and treated with co-trimoxazole and paracetamol.

Consider the following—

- What is the possibility of the patient having an ADR in addition to the acute respiratory infection?
- If you think it is an ADR, which medicine or medicines might be responsible? How did you arrive at this conclusion?
- What kind of action by the DTC is warranted in this case?

Activity 3. Serious ADRs with Phen-Fen Combination Medicine

The combination medicine phenteramine and fenfluramine (commonly called phen-fen) was a popular diet medicine throughout Europe and North America. Like all anti-obesity medicines, this combination leads to tolerance after several months of use, and weight gain invariably occurs when the medicine is discontinued. Short-term effectiveness was dramatic, however, with countless success stories and many patients demanding prescriptions. Safety of this combination was confirmed through the usual premarketing clinical trials. Because phen-fen was another
weight control product, testing and evaluation were extensive, and the approval process was not fast-tracked. Soon after the marketing of the medicine, spontaneous reports began to appear describing serious cardiovascular problems including valvular heart disease and pulmonary hypertension. Spontaneous reports continued until it became obvious that the combination was highly suspect for causing the adverse effect.

- What are some other possible causes for the cardiac conditions listed in the activity?
- What would have prevented this serious side effect from being detected in premarketing trials?
- Why would spontaneous reports be so effective in detecting this ADR after phen-fen’s distribution to the general market?

**Summary**

Medicine safety issues are critical to a health care system. The DTC is in a position to have a significant impact on preventing and managing these problems. The DTC should have appropriate people to assess the literature carefully to determine the safety of medicines for the formulary. Appropriate management of ADRs should include—

- Assessing the safety of all new medicines before placing them on the formulary
- Implementing systems to monitor the occurrence of ADRs
- Managing and evaluating suspected ADRs, assigning causality and taking corrective action when necessary
- Reporting ADRs to regulatory authorities and manufacturers
- Preventing the occurrence of ADRs and events by—
  - Monitoring the health care system through ADR reporting
  - Carefully evaluating patients before prescribing medications, especially high-risk patients or patients on high-risk medicines
  - Educating staff, especially providers, concerning possible reactions
Annex 1. Adverse Drug Reaction Reporting Form  
(for hospital and primary care clinic use only)

<table>
<thead>
<tr>
<th>Patient and Reaction Information</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Date</td>
<td></td>
</tr>
<tr>
<td>Name</td>
<td></td>
</tr>
<tr>
<td>Chart number</td>
<td></td>
</tr>
<tr>
<td>DOB</td>
<td></td>
</tr>
<tr>
<td>Physician</td>
<td></td>
</tr>
<tr>
<td>Medicine</td>
<td></td>
</tr>
<tr>
<td>Diagnosis for use (indications)</td>
<td></td>
</tr>
<tr>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>Date medicine started</td>
<td></td>
</tr>
<tr>
<td>Date of reaction</td>
<td></td>
</tr>
<tr>
<td>Relevant medical history</td>
<td></td>
</tr>
<tr>
<td>including concurrent pharmaceutical therapy</td>
<td></td>
</tr>
<tr>
<td>Description of ADR</td>
<td></td>
</tr>
<tr>
<td>Outcomes attributed to ADR</td>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
<td>3.</td>
</tr>
<tr>
<td>4.</td>
<td></td>
</tr>
<tr>
<td>Probability of reaction</td>
<td></td>
</tr>
<tr>
<td>Severity code (see definitions below)</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td>Minor</td>
<td></td>
</tr>
<tr>
<td>Incidental</td>
<td></td>
</tr>
<tr>
<td>DTC action—</td>
<td></td>
</tr>
<tr>
<td>• Mark patient’s chart</td>
<td>Yes</td>
</tr>
<tr>
<td>• Discuss with prescriber</td>
<td>Yes</td>
</tr>
<tr>
<td>• Add to database</td>
<td>Yes</td>
</tr>
<tr>
<td>• Report to NDA</td>
<td>Yes</td>
</tr>
<tr>
<td>• Report to manufacturer</td>
<td>Yes</td>
</tr>
<tr>
<td>Report initiated by:</td>
<td></td>
</tr>
<tr>
<td>Date:</td>
<td></td>
</tr>
</tbody>
</table>
# Severity Assessment Guide

<table>
<thead>
<tr>
<th>Severity of ADR</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>Fatal or life threatening</td>
</tr>
<tr>
<td>Moderate</td>
<td>Requires antidote, medical procedure, or hospitalization</td>
</tr>
<tr>
<td>Mild</td>
<td>Symptoms are evident and require only the discontinuation of pharmaceutical therapy</td>
</tr>
<tr>
<td>Incidental</td>
<td>Mild symptoms; patient is given option to continue or discontinue</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do Not Know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the adverse event appear after the suspected medicine was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Did the adverse reaction improve when the medicine was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the adverse reaction reappear when the medicine was re-administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
</tr>
<tr>
<td>Are there alternate causes (other than the medicine) that could solely have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
</tr>
<tr>
<td>Was the medicine detected in the blood (or other fluids) in a concentration known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the reaction more severe when the dose was increased or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Did the patient have a similar reaction to the same or similar medicines in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Was the adverse event confirmed by objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Total the score to determine the category of the reaction. The categories are defined as follows—

- **Definite**: > 9
- **Probable**: 5–8
- **Possible**: 1–4
- **Doubtful**: 0