DRAFT ASHP Guidelines on Adverse Drug Reaction Monitoring and Reporting

Pharmacists are uniquely positioned to provide the knowledge and expertise needed to develop and organize comprehensive programs that monitor and report adverse drug reactions (ADRs) in health systems. ADR monitoring and reporting programs (hereinafter, "ADR programs") encourage ADR surveillance, facilitate ADR documentation, promote reporting of ADRs, provide mechanisms for monitoring the safety of drug use, and stimulate the education of healthcare professionals regarding potential ADRs. In addition, ADR programs focus on causative factors that may lead to ADRs, plan for preventive actions, and measure the results of these changes.

The purpose of this document is to provide updated guidance for organizations initiating an ADR program or seeking to improve an existing program. The following topics are covered: common definitions, recommended program features, program goals, and the pharmacist's role in the development of a comprehensive program. The recommendations in these guidelines represent a consensus of professional judgment, expert opinion, and documented evidence. They are written to establish reasonable goals, to be progressive and challenging, yet attainable as best practices in applicable settings. They do not represent minimum levels of practice, and pharmacy professionals are encouraged to exercise their professional judgment in assessing and adapting these recommendations to meet the specific needs of their healthcare organizations.

Definitions

Adverse event (AE): any undesirable experience associated with the use of a medical product in a patient.[1]

Adverse drug event (ADE): harm resulting from medical intervention involving a drug, irrespective of drug dose.[2-4]

Adverse drug reaction (ADR): Several definitions of ADR are provided below. Although healthcare organizations may need to apply ADR surveillance to different degrees for different patient populations, it would be beneficial if a common definition of ADR were used in all settings to facilitate reporting, collective surveillance, and ADR-trend research.

- *World Health Organization* (WHO): 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.[2]
- *Karch and Lasagna*: Any response to a drug that is noxious and unintended, and that occurs at doses used in humans for prophylaxis, diagnosis, or therapy, excluding failure to accomplish the intended purpose.[5]
- *Food and Drug Administration* (FDA): For reporting purposes, FDA categorizes a *serious adverse event* (events relating to drugs or devices) as one in which "the patient outcome is death, life-threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage."[1]

To contrast ADRs and ADEs, an ADR (using the WHO definition) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in patients for prophylaxis,

diagnosis, or treatment of a disease, or for the modification of physiological function, whereas an ADE is an injury resulting from medical intervention involving a drug, independent of drug dose.[2,3] Given these definitions, all ADRs are a type of ADE, but not all ADEs are ADRs. ADRs are a narrow subset of ADEs and should therefore be monitored separately. Drug withdrawal, drug-abuse syndromes, accidental poisoning, and drug-overdose complications should not be defined as ADRs.

In the previous version of these guidelines, ASHP offered the following definitions of different types of ADRs.[6]

1. Significant ADR: an ADR that
    a. Requires discontinuing the drug (therapeutic or diagnostic);
    b. Requires changing the drug therapy;
    c. Requires modifying the dose (except for minor dosage adjustments);
    d. Necessitates admission to a hospital;
    e. Prolongs a stay in a healthcare facility;
    f. Necessitates supportive treatment;
    g. Significantly complicates diagnosis;
    h. Negatively affects prognosis; or
    i. Results in temporary or permanent harm, disability, or death.
2. Allergic ADR: an ADR that results from an immunologic hypersensitivity.
3. Idiosyncratic ADR: an ADR that is peculiar to the individual.

Side effect: An expected, well-known reaction resulting in little or no change in patient management (e.g., drowsiness or dry mouth due to administration of certain antihistamines or

nausea associated with the use of antineoplastics); an effect with a predictable frequency and an effect whose intensity and occurrence are related to the size of the dose.[6]

Trigger tools: Chart review, via automated or manual processes, to detect "triggers" that may be representative of an ADE or ADR.[7] The trigger is investigated to determine if an ADE occurred (e.g., an INR >7 is the trigger, the chart is then reviewed to determine if warfarin is the cause).

Trigger medications: Medications commonly used to treat ADRs, such as antidotes, reversal agents, steroids, or antihistamines.[7]

High-alert drugs: Drugs that bear a heightened risk of causing significant patient harm when they are used in error.[8]

Natural language processing: computer software analysis of text contained in the electronic health record (EHR) to identify possible ADRs.[9]

Goals of an ADR program

The primary goal of an ADR program should be to reduce the risk and severity of ADRs. An ongoing ADR program can provide benefits to the organization, patients, pharmacists, and other healthcare professionals, including (but are not limited to) the following.

1. Improving patient care and decreasing length of stay by ensuring safer use of drugs.
2. Educating healthcare professionals and patients about drug effects and increasing their level of awareness regarding ADRs.
3. Providing an indirect measure of the quality of drug therapy through identification of preventable ADRs and anticipatory surveillance for high-risk drugs or patients.

4. Complementing organizational risk-management activities and efforts to minimize liability.
5. Assessing the safety of drug therapies, especially recently approved drugs.
6. Providing quality-assurance screening findings for use in medication-use evaluation programs.
7. Measuring the economic impact of ADR prevention as manifested through reduced hospitalization, optimal and economical drug use, and minimized organizational liability.
8. Measuring ADR incidence. (ASHP does not suggest that there is a predictable rate of incidence or severity of ADRs. The number and severity of ADRs in a given organization or setting would vary with the organization's size, type, patient mix, drugs used, modalities utilized to assess risk and patient harm, and the ADR definition used.)

ADR program features

A comprehensive ADR program should be an integral part of an organization's overall drug-use system and should include the following features (Figure 1).

1. A surveillance system that spans the course of the medication-use process.
    a. An ongoing and concurrent (during drug therapy) surveillance system based on the reporting of suspected ADRs by pharmacists, physicians, nurses, other caregivers, and patients.[10]
    b. A prospective surveillance system for high-risk drugs or patients at high risk for ADRs.

c. A retrospective surveillance system to identify potential ADRs. This surveillance would include identifying alerting orders for the use of trigger medications that are used to treat common ADRs (e.g., orders for immediate doses of antihistamines, epinephrine, or corticosteroids), abrupt discontinuation or decreases in dosage of a drug, or stat orders for laboratory assessment of therapeutic drug levels.[11-14]

d. Tools such as event monitoring and natural language processing can be used to detect certain types of adverse events in clinical databases.[15,16]

2. Prescribers, caregivers, and patients should be notified following institutional policy and procedures regarding suspected ADRs.

3. Information regarding suspected ADRs should be reported to the pharmacy department for complete data collection and analysis, including the patient's name, the patient's medical and medication history, a description of the suspected ADR, the temporal sequence of the event, and any remedial treatment required.[10]

4. High-risk patients should be identified and monitored.

   a. High-risk patients include but are not limited to pediatric patients, geriatric patients, patients with organ failure (e.g., hepatic or renal failure), and patients receiving multiple drugs.[11]

5. High-alert drugs should be identified, and their use should be routinely monitored. Examples of drugs that may be considered as high-alert include aminoglycosides, amphotericin, antineoplastics, corticosteroids, digoxin, heparin, lidocaine, phenytoin, theophylline, thrombolytic agents, and warfarin.[8,11]

6. The cause(s) of each suspected ADR should be evaluated on the basis of the patient's medical and medication history, the circumstances of the ADR, the results of dechallenge and rechallenge (if any), alternative etiologies, and a literature review.
7. A method for assigning the probability of a reported or suspected ADR should be developed to categorize each ADR. Many algorithms to assist in assessment of the cause of the ADR have been developed. Commonly used algorithms include the Naranjo algorithm, WHO causality tool, and the Liverpool ADR causality tool; however, there are many others that pharmacists may find useful.[5,17-24] Subjective questions and the professional judgment of a pharmacist can be used as additional tools to determine the probability of an ADR. Questions might include the following.
    a. Was there a temporal relationship between the onset of drug therapy and the adverse reaction?
    b. Was there a dechallenge (i.e., did the signs and symptoms of the adverse reaction subside when the drug was withdrawn)?
    c. Can signs and symptoms of the adverse reaction be explained by the patient's disease state?
    d. Were there any laboratory tests that provide evidence for the reaction being an ADR?
    e. What was the patient's previous general experience with the drug?
    f. Did symptoms return when the drug was re-administered?
8. A method for ranking ADRs by severity should be established. A commonly used scale ranks severity into seven categories according to clinical consequence, including

resultant harm and intensity of medical intervention required.[25] The National Cancer Institute Common Terminology Criteria for Adverse Events is a standardized system to quantify or grade the severity of adverse medication reactions.[26] The National Coordinating Council for Medication Error Reporting & Prevention also provides a classification that can assist in coding ADEs; it considers factors such as whether the error reached the patient and whether the patient was harmed and to what degree.[27]

9. A description of each suspected ADR and the outcomes from the event should be documented in the patient's medical record.
    a. Some EHRs do not readily distinguish between an allergy and significant ADR without additional investigation into the record by the clinician.[15,16]
    b. ADR monitoring and reporting programs should take into consideration the limitations and advantages of the available EHR to ensure timely and appropriate information are provided to clinicians.
10. Serious or unexpected ADRs should be reported to a medication manufacturer and/or the FDA.
    a. Manufacturers will request detailed information about the drug product involved and patient case, so it is important to sequester as much evidence and clinical information as possible prior to reporting.
    b. FDA offers two online reporting tools, MedWatch[28] and the Vaccine Adverse Event Reporting System (VAERS),[29] which can be used to report events and follow signals.

11. All ADR reports should be reviewed and evaluated by a designated interdisciplinary committee (e.g., pharmacy and therapeutics committee).
    a. In settings where it is possible, a pharmacy-coordinated ADR team or committee, consisting of a physician, nurse, quality improvement leader, an administrator, and a pharmacist is recommended.[30-32]
    b. The team should be charged with adopting a definition for the organization, promoting awareness of the consequences of ADRs, establishing mechanisms for identifying and reporting ADRs, reviewing ADR patterns or trends, and developing preventive and corrective interventions.
12. ADR report information and trending should be disseminated to healthcare professional staff members for educational purposes, while maintaining patient confidentiality. Suggested topics for medical staff education include recognition of ADRs and appropriate and effective care for patients who experience ADRs. Educational programs can be provided in various formats, such as morning report/safety huddle discussions, newsletters, grand rounds presentations, algorithms for treatment, and interdisciplinary reviews of medication-use evaluations.
13. Findings from an ADR program should be incorporated into the organization's ongoing quality improvement activities. The process should include the following actions.
    a. Feedback to all appropriate healthcare staff, patients, and caregivers.
    b. Continuous monitoring for trends, clusters, or significant individual ADRs, both internally and externally.

i. Internal data can be trended by patient demographics (e.g., gender and age), patient care area, involved drug(s) and drug class, reaction type, and severity level. Data can be reported via descriptive analysis or as a trend (Figures 2-4 provide examples).

ii. The FDA Adverse Event Reporting System (FAERS) can be utilized for trending external data through its public dashboard.[33]

c. Educational efforts for detection, prevention, and reporting of ADRs.

d. Evaluation of prescribing patterns, patient monitoring practices, patient outcomes, and the ADR program's effect on overall and individual patient outcomes.

Role of the pharmacist in ADR monitoring and reporting

Pharmacists are a vital link between the patient and the health system before and during the course of drug therapy.[34,35] Pharmacists are uniquely qualified to provide valuable information on drug products and can play an important role in monitoring adverse events in health systems.[36,37]

Pharmacists should obtain formal endorsement or approval of such programs through appropriate committees (e.g., a pharmacy and therapeutics committee and the executive committee of the medical staff) and the organization's administration. In applicable settings, input into the design of the program should be obtained from the medical staff, nursing staff, quality improvement staff, medical records department, and risk managers.[20,38-40]

The pharmacist should facilitate the following activities:

1. Analysis of each reported ADR;
2. Identification of drugs and patients at high risk for being involved in ADRs;
3. The development of policies and procedures for the ADR-monitoring and reporting program;
4. A description of the responsibilities and interactions of pharmacists, physicians, nurses, risk managers, and other health professionals in the ADR program;
5. Use of the ADR program for educational purposes;
6. Development, maintenance, and routine evaluation of ADR records within the organization, including the use of standardized reporting rate and incidence of onsite ADRs occurrence;
7. The organizational dissemination and use of information obtained through the ADR program;
8. Reporting of serious ADRs to the FDA, the manufacturer, or both; and
9. Publication and presentation of important ADRs to the medical community.

Conclusion

Pharmacists are uniquely positioned to assist in the coordination of an ADR program. Programs should focus on surveillance (both prospective and retrospective), complete documentation within medical records, reporting to and review by an interdisciplinary committee, and education to achieve an overall goal of reducing the risk and severity of ADRs within an organization. All direct patient care pharmacists should understand their role in recognizing, evaluating, reporting, and educating both patients and providers on ADRs.

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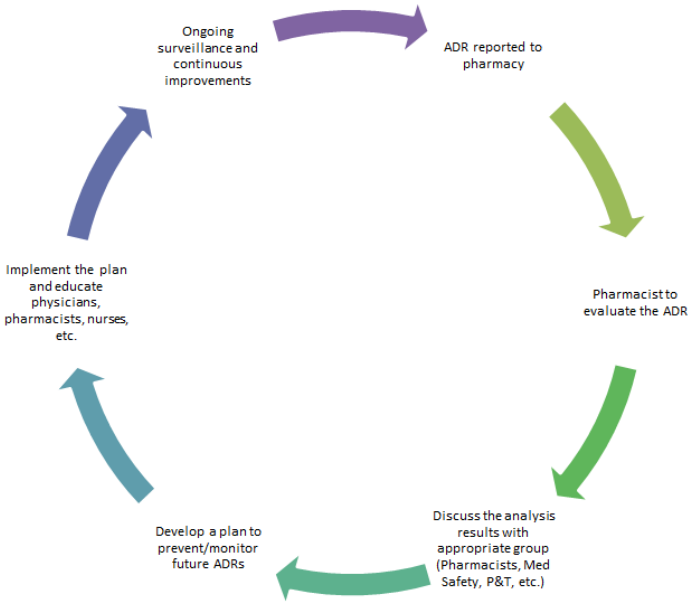

Figure 1. Features and process of a comprehensive adverse drug reaction (ADR) monitoring and reporting program. Med Safety, Medication Safety Committee (or similar organization); P&T, Pharmacy and Therapeutics Committee (or similar organization).

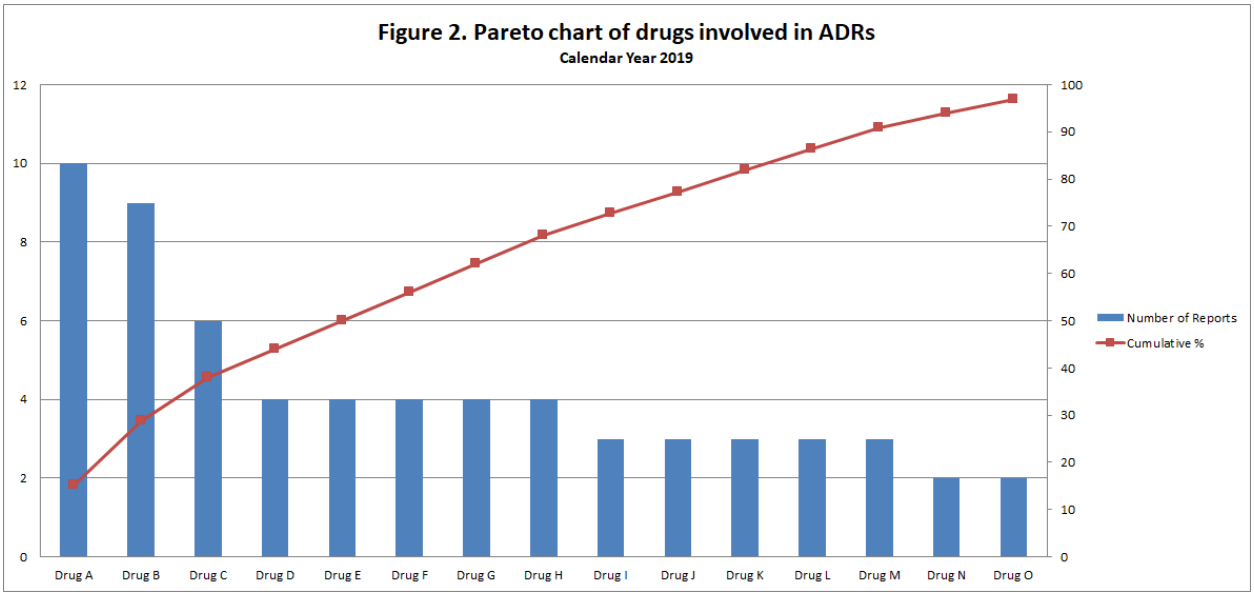

Figure 2. ADR trending by involved drug using Pareto principle. In the example, Drug A was the top reported medication involved in ADR events which can be used as a signal to warrant additional investigation.

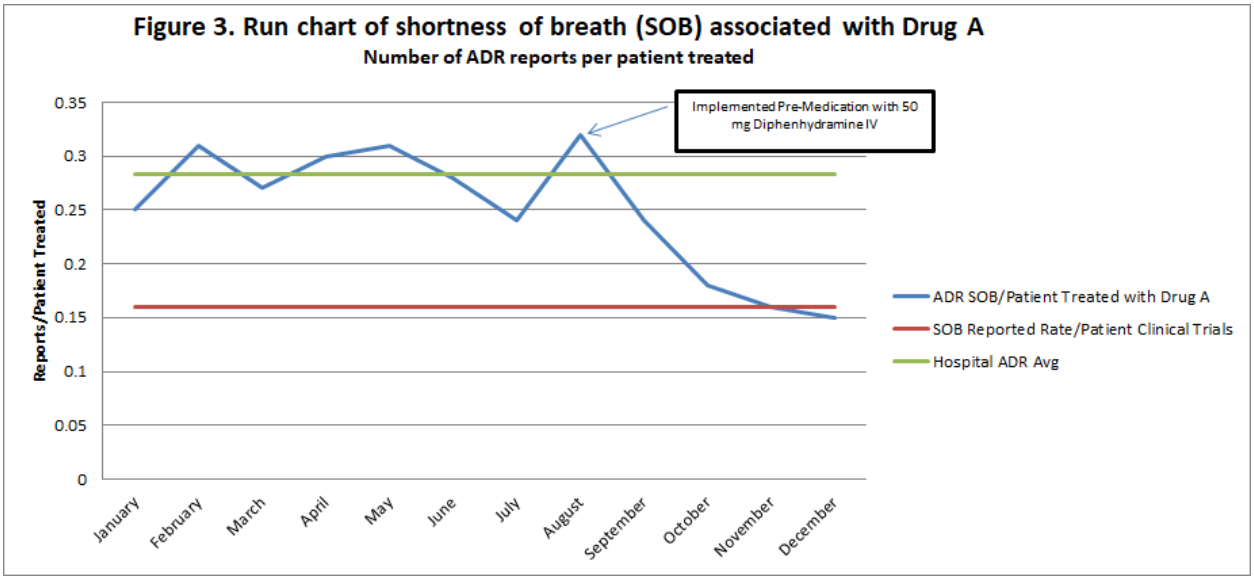

Figure 3. Example of monthly ADR event trending of the top reported medication identified in Figure 2. In the example, shortness of breath (SOB) ADR involving Drug A were captured on a monthly basis. Comparison was made to the hospital's ADR average (green line) and reported SOB events resulting from the use of Drug A as reported in clinical trials (red line). Based on the trends noted, an intervention was made in August to premedicate patients and this milestone is depicted on the graph.

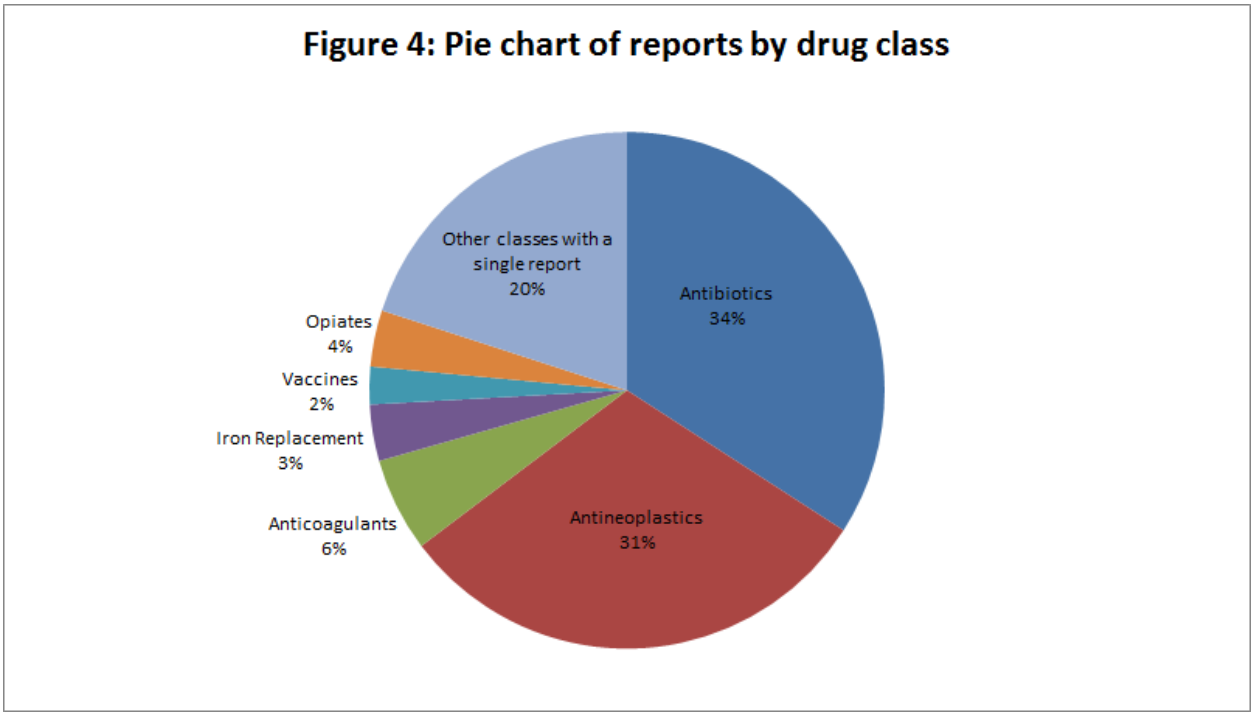

Figure 4. Example of reported ADR events by involved drug class organized in a pie chart.