A BRIEF OVERVIEW OF ADVERSE EVENT REPORTING

Dr. Wangui Mathenge, Qualified Person for Pharmacovigilance Sub Sahara Africa

Summary

In the world of pharmacovigilance (PV), adverse drug reactions (ADRs) and adverse events (AEs) hold separate definitions. These two terms are not synonymous to each other. However, to draw comparisons, an AE is somewhat a more general term that means any untoward reaction an individual experiences after taking medication. An ADR on the other hand is a more specific term and this reaction is usually qualified by circumstances that show that the untoward/unwanted reaction has a causal relationship with the medication taken.

To illustrate ADRs and AEs, we take a case of a patient who took drug X in the morning for pain and a few hours later was involved in a road traffic accident. In this case, we consider the road traffic accident as an AE until qualified otherwise. On the other hand, a patient who took drug X in the morning for pain and three hours complained of slight dizziness. Since he took drug X from a new pack he had opened, he assumed it was something else he ate and disregarded the dizzy spell and drove his car to attend a meeting. Three kilometers away from the start of his journey, he became unconscious while driving and was involved in a road traffic accident. This incidence should be considered to be as a result of an ADR.

1.0 Introduction:

International Conference on Harmonization (ICH) defines an *Adverse Event (AE) as any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a medicinal product, whether or not considered related to this medicinal product.*

Adverse drug reactions (ADR), as established by regional regulations, guidance, and practices, concern noxious and unintended responses to a medicinal product. The phrase "responses to a medicinal product" means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. A reaction, in contrast to an event, is characterized by the fact that a causal relationship between the drug and the occurrence is suspected. For regulatory reporting purposes, if an event is spontaneously reported, even if the relationship is unknown or unstated, it meets the definition of an adverse drug reaction. [(1)]

From the above scenarios, it is still not so easy to know for sure without thorough follow up investigations whether the second example is an adverse drug reaction, hence there is a need for thorough ADR/AE management.

According to European Medicines Agency (EMA)[2], the Food and Drug Administration (FDA) [3] and locally, the Pharmacy & Poisons Board (PPB)[4], it is a requirement for all Marketing Authorization Holders (MAHs) to employ adequate pharmacovigilance measures to ensure they assume responsibilities for all their registered and marketed products and provide necessary actions when need arises.

Therefore, it is the responsibility of the MAH to document AEs, conduct thorough follow ups for investigations, process and analyze or upgrade an AE to an ADR due to findings received, and submit the report to the Health Authorities (HA) in an expedited manner either in the Council for International Organizations of Medical Sciences (CIOM) or in E2B format depending on the HAs requirements. This report is now referred to as an Individual Case Safety Report (ICSR).

2.0 Classification of an ICSR

An ICSR can be classified as follows as either serious or not serious, and expected or unexpected. A serious AE/ADR (SAE/SADR) is any untoward reaction observed after taking medication at any dose and results in a medically significant/important event like convulsions, initial/prolonged hospitalization, persistent/significant disability or impairment, congenital anomaly/birth defect, and death.
A non serious AE/ADR (NSAE/NSADR) is any other untoward reaction observed after taking medication at any dose and does not meet any of the above SAE/SADR criteria.

The seriousness criteria of an AE/ADR is not chosen due to the severity or intensity of an event/reaction. For example, if drug Y has been identified to cause a headache and the product label classifies headache as an expected AE, then if a patient/health care professional reports that a headache has increased in intensity to a "severe" headache/migraine then the category of this AE/ADR will remain as non-serious, provided the headache does not lead to any of the above SAE/SADR classification.

An expected AE/ADR is an AE/ADR whose nature, severity, specificity or outcome is consistent with the terms or description used in the products labeling tools such as the Summary of product characteristics (SmPC) or the package insert leaflet (PIL)[1]. An unexpected AE/ADR is an AE/ADR whose nature, severity, specificity or outcome is not consistent with the term or description used in the products labeling tools [1].

The MAH should categorize an Expected AE/ADR that leads to death as UNEXPECTED, unless this was already noted in the labeling material that the noted AE/ADR was expected to cause a fatal outcome. [1]

It is important to note other terminologies used to categorize AEs. For instance, an Adverse Event Following Immunization (AEFI) is any untoward medical occurrence which follows immunization, and does not necessarily have a causal relationship with the usage of the vaccine. If not rapidly and effectively dealt with, it can undermine the confidence in a vaccine and ultimately have dramatic consequences for immunization coverage and disease incidence. [5, 6]

Immunization anxiety-related reaction is an adverse event following immunization arising from anxiety about the immunization. [6]

On the other hand, immunization error-related reaction is an adverse event following immunization that is caused by inappropriate vaccine handling, prescribing or administration. By its nature, this type is an AE which is very preventable. [6]

3.0 Sources of ICSR

An ISCR can be received from solicited or unsolicited sources. Two major sources of ICSR are described hereafter.

3.1. Solicited ICSR

These are organized data collection systems, which include clinical trials, program registries, post authorization named patients use /compassionate use programs, market research, patient support and disease management programs, surveys of patients or healthcare providers or information gathering on efficacy or patient compliance.

For the purpose of safety reporting, solicited reports should not be considered spontaneous but classified as an ICSR from studies and therefore should have an appropriate causality assessment by a healthcare professional or the MAH. [1, 6]

3.2. Unsolicited ICSR

These are unsolicited communications by a healthcare professional or consumer to a company, regulatory authority or other organization that describe an adverse reactions in a patient who was given a medicinal product. It does not derive from a study or any organized data collection scheme.[1, 6]

Notable sources of unsolicited ICSRs are received from health care professionals, company representatives, literature, internet, lay press/media, lawyers, patient group associations, amongst others.

4.0 Minimum Criteria for ICSR [6, 7]

For a case to qualify as a valid ICSR, the minimum criteria that must be met in the report is described in Table 1.

Table 1. Minimum Criteria for a Case to Qualify as an ICSR

- A patient identifier (this could be either the Age/group, sex, race, patient file/program number or weight/height).

  It is unethical to put the patients name or passport/national identification numbers in an ISCR report.
- A known reporter (this includes the full name, occupation, place of occupation, address and contact details)
- Suspected product. The suspected company's product, associated to the event either in its proprietary name or non-proprietary name should be documented.

- A stated event. This should always be reported in the patient's verbatim and where applicable, a translation should be made according to the HA language requirements. The purpose of using the patient's verbatim is to avoid exaggeration or "*medical knowledge"* biased errors that may tend to lessen the event in AE reporting.

Other criteria that can be added in a valid ICSR report include;

- Laboratory findings.
- Concomitant medication/products
- Medication/products used to treat the AE.
- Country of occurrence
- Details of the MAH
- Type of the ICSR (Initial or follow-up)

5.0 Time Frames for ICSR Reporting

While calculating ICSR time frame, it is important to note that the day a valid ICSR has been identified/received by the MAH, that day is termed as day zero (Day 0).

As a general rule, all valid AEs should be reported as soon as possible but not later than 15 calendar days. [(7)]

According to articles 107 (3) and 107a (4) of Directive 2001/83/EC [(8)] and articles 107a (4) of Directive 2010/84/EU [(9)], it is expected that all serious valid ICSRs should be reported within 15 days following receipt of the report whereas, the MAH is expected to report all Non-serious ICSRs within 90 days.

Locally, the Pharmacovigilance (PV) Department at the Pharmacy & Poisons Board has acknowledged that the MAH should report all valid serious ICSRs within 7 Calendar days and all non-serious ICSRs to be reported within 15 Calendar days. [(10)]

In order to adhere to these regulatory requirements, the MAH should device a time frame PV system that should be able to cover all aspects of ICSR report management. One should consider this period, from the day the AE is first noted, to assessment and processing, to subsequent follow ups, transmission to and from the company central reservoir and finally, relaying the ICSR according to the HA formatting process.

Most MAHs that observe regulatory and safety compliance, recommend AE reports from all other company's stakeholders be reported to the company's Qualified Person for PV(QPPV) either within 24 hour or 1 business day from the date the AE report was received. However, this is subjective to the individual company's pharmacovigilance policies.

6.0 Adverse Events

Table 2 indicates incidences through which an AE can occur.

Table 2. Incidences for the Occurrence of AE

a) Use of the medicinal products within the terms defined by the MAHs
b) Use of the medicinal products outside the terms defined by the MAH like;
    i. Overdose
    ii. Off-Label Use
    iii. Misuse
    iv. Abuse
    v. Suspected Transmission of an Infectious Agent (STIAMP)
    vi. Lack of efficacy
c) Occupational Exposure.
d) Pregnancy*
e) Breast feeding*
f) Substandard/Spurious/Falsely Labeled/Falsified/Counterfeit Medicinal Products

**** While pregnancy and breastfeeding are not Adverse Events, it is during those stages that an AE/ADR can potentially occur to the fetus/neonate/infant while the mother/father is taking a suspected product.***

7.0 Marketing Authorization Holder PV System

An AE report management forms the basis of any pharmacovigilance system /department of the MAH. Even though AE reporting is an integral and primary part of a pharmacovigilance system, it is not the only activity conducted.

Table 3. Activities that Cascade from ICSR Reporting

1. Oversight of all contractual agreements between the MAH and any service provider that the company may contract to handle its products. This action leads to incorporation of a Pharmacovigilance Agreement that outlines the MAH's PV requirements and obligations.
2. Management and maintenance of the Development Safety Update Reports (DSURs).
3. Management and maintenance of the Periodic Benefit Risk Evaluation Reports (PBRERs) for EU based organizations or Periodic Adverse Drug Experience Reports (PADERs) for US based organizations.
4. Management and maintenance of Risk Management Plans (RMPs for EU) and Risk Minimization activities (RMiNA for US).
5. Management and maintenance of Incident Management Plans.
6. Annual Safety Reports for clinical trial sites reporting to the Ethics committees (EC) or Institutional Review Board (IRB).

7. Maintain oversight for Dear Health Care Professional communication (DHPC).
8. Maintain oversight for To Whom It May Concern communication (TWIMCL).
9. Signal detection Management.
10. Enhance Pharmacovigilance legislation and Directives.
11. Maintain and manage oversight of medicines under additional monitoring.
12. Management and maintenance of Post Authorization Safety Studies (PASS).
13. Maintain the product labeling tools.
14. Update and maintain the Reference Safety information (RSI).
15. Update and maintain the Company Core Data Sheet (CCDS).
16. Update and maintain the Company Core Safety Information (CCSI).
17. Maintenance of the Pharmacovigilance System Master File (PSMF).
18. Oversight of safety Quality Management System.

Therefore, it becomes paramount for all stakeholders and citizens to ensure that even as AE reporting is not only being done to the regulatory authority, but additionally, a copy of that AE report must also be submitted to the affected MAH for further action.

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