

Comparative evaluation of adverse drug reaction reporting forms for introduction of a spontaneous generic ADR form

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ABSTRACT

Despite comprehensive and stringent phases of clinical trials and surveillance efforts, unexpected and serious adverse drug reactions (ADRs) repeatedly occur after the drug is marketed. ADR reporting is an important aspect of an efficient and effective pharmacovigilance program. Although Medwatch, Yellow Card, CDSCO form, etc. are the protocol forms of ADR collection and reports, a number of countries design and use their respective ADR forms. This review compares similarities and dissimilarities of 13 ADR forms of countries representing their geographical location. This study extracted 73 data elements mentioned in 13 different ADR forms. Only 13 elements were common. An ADR form of Malaysia and Canada covers the highest number of data 43, while Brazil falls to the opposite end with a number of 17 data elements *in lieu* with the Generic ADR Form. The result of this review highlights 58 data elements of the proposed generic ADR form which ensures that requisite reporting information essential for correct causality assessment of ADRs are included. The proposed "Generic ADR form" could be adopted worldwide mandatorily for reporting any/all ADRs associated with marketed drugs.

Key words: Causality assessment, generic form, pharmacovigilance

INTRODUCTION

Reporting of an adverse drug reaction (ADR) is a critical parameter of medical treatment. ADRs are one of the leading causes of morbidity and mortality, adding to overall healthcare cost. It is estimated that approximately 2.9–5.6% of all hospital admissions are caused by ADRs and as many as 35% of

hospitalized patients experience an ADR during their hospital stay.^[1] The overall incidence of serious ADRs is 6.7% and of fatal ADRs is 0.32% in hospitalized patients, making these reactions between the fourth and sixth leading cause of death, respectively.^[2] Hence, the impact of ADRs on patient safety, health cost, and improved public health in relation to use of medicines by the provision of reliable and balanced information resulting in more rational use of medicines lead to emergence of a new medical discipline known as pharmacovigilance (PV). PV is defined as the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug-related problem.

The World Health Organization (WHO) defines an ADR as "a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis,

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diagnosis, or therapy of disease, or for the modification of a physiological function".^[3] There are various methods of ADR monitoring such as prescription event monitoring, case report/case series, etc.; however, spontaneous ADR reporting is the widely used. It is particularly useful in identifying rare and delayed reactions.

At present, the WHO International Drug Monitoring program has 104 countries as official members and 29 countries as associate members.^[3] ADR reports from various member nations are forwarded to Uppsala Monitoring Centre (UMC) where they are processed, evaluated, and entered into the WHO International database. However, all member countries have different forms of varied parameters, resulting in ambiguity of the collected ADR. For proper evaluation, assessment and processing of the ADR report and to establish causal relationship between the suspected drug and the adverse reaction, ADR reporting form should be consistent, comprehensive, and conclusive.

CURRENT SCENARIO

Currently, there is not a single standard reporting format recognized internationally for submission of the ADR case information to the UMC or to the national PV centers. Council for International Organizations of Medical Sciences (CIOMS) reporting form is the only internationally recognized format, which was designed in 1990 for reporting the ADR case information to the regulatory body. This form was developed for providing ADR information on the new molecules which are under clinical trial by Marketing Authorization Holders (MAH) to regulatory body, but it does not solicit case information from health professionals.

At present, there are two internationally recognized formats for reporting the individual case safety report (ICSR). One is International Conference on the Harmonisation (ICH) E2B standard format which is used for the exchange of case information between MAH and regulators. The second is the WHO reporting form, developed in 1968 to exchange ICSR between national PV centers and WHO known as 'Vigibase'. Since 2001 this paper reporting format is converted to an online electronic format known as Vigimed (an online E-mail conferencing facility, exclusive to member countries of the WHO Program for International Drug Monitoring). Both these formats are electronic formats having their respective advantages and disadvantages. They cannot be converted to a paper format as they are extensive and not useful for collection of original data from health-care professionals. The WHO-Quality Assurance and Safety of Medicines (QSM) team has recently received request from the public health program involved in the establishment of PV system in many countries across the world for a general WHO form, used for spontaneous reporting of ADR.^[4]

This review presents a comprehensive and conclusive generic ADR form which includes all the requisite reporting information for correct causality assessment, which could be accepted mandatorily globally for reporting adverse reactions of marketed drugs.

MATERIALS AND METHODS

ADRs forms of various countries (13 in the present case) were selected from six continents. ADR reporting forms of 13 different countries, including Argentina,^[5] Brazil,^[6] Australia,^[7] New Zealand,^[8] United States,^[9] Canada,^[10] India,^[11] Malaysia,^[12] Singapore,^[13] United Kingdom,^[14] Sweden,^[15] Kenya,^[16] and South Africa,^[17] were collected from the internet and comparative evaluation was carried out. For evaluating the forms, data elements were categorized into six parameters: (1) patient information, (2) hospital/clinic details, (3) suspected drug details, (4) adverse reaction details, (5) concomitant drug details, (6) reporter details, and (7) additional information.

RESULTS AND DISCUSSION

Seventy-three different data elements were found in 13 reporting forms [Table 1] of which 13 elements were common. These were patients age or date of birth, suspected drug name, its dose, start and stop date of suspected drug, date of onset of ADRs, description of ADR, outcome, name of concomitant drug, reporter name, address, and phone number.

The presence of only 13 common data elements depicts a significant variability in the content of the various reporting forms of different countries namely Medwatch, Yellow Card, CDSCO, etc. Patient's demographic variable which includes patient's age, sex, body weight, height, body mass index (BMI), and body surface area (BSA) is an important parameter for evaluating an ADR. Although the age was mentioned in all ADR forms, other details were not reported. BMI and BSA determine the correct dosage for a particular individual, especially for drugs with low therapeutic index. Patient's weight and height determine BMI and BSA which makes their mention important. Another parameter of special consideration is ethnicity, which emphasizes the diversity of different ethnic groups to associated risk factors. For example, according to a study, relative ratio (RR) of cough from angiotensin converting enzymes (ACE) inhibitors for East Asian compared with white patients is 2.7.^[18]

Similarly sex, patient's medical history, allergic status, relevant laboratory data, pregnancy status, and habits of patients are important contributing parameters assessing causality. Suspected and concomitant drug details are essential for assessment of reported ADR. Suspected drug

Table 1: Comparative evaluation of ADRs forms of 13 countries**Parameters Countries Following****Patient information**

Name/initial: AR, BR, AU, NZ, IN, MY, SG, UK, SE, KE, SA
 Pt. address: NZ
 Age: AR, BR, AU, US, CA, IN, MY, SG
 Sex: AR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Date of birth: AU, NZ, US, IN, SE, KE, SA
 Ethnicity: NZ, US, IN, MY, SG
 Height: CA, SE, KE, SA
 Weight: AR, AU, US, CA, IN, MY, SG, UK, SE, KE, SA
 Identification no: AU, NZ, US, CA, SG, UK, KE
 Pregnancy status: AR, US, CA, IN, SG, KE
 Diagnosis: AR, US, CA, IN, KE
 Relevant history: BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, SA
 Lab data: AR, AU, US, CA, IN, MY, UK, SA
 Liver/kidney function test: AR, NZ, US, CA, IN, MY, SG, UK
 Previous drug exposure: AU, SA
 Smoking and alcohol: AR, BR, AU, NZ, US, CA, IN, SG, UK

Hospital/clinic details

Name of Institute: KE
 Place of practice: MY
 Institute address: KE
 Contact details: KE

Suspected drug details

Drug: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Strength: US, CA, SE, SA
 Name of manufacturer: BR, US, CA, IN, MY
 Batch no.: AR, NZ, US, CA, IN, MY, SG, UK
 Expiry date: US, CA, IN
 Dosage form: SE, SA
 Dose: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Route of administration: AR, NZ, US, CA, IN, MY, SG, UK, KE, SA
 Frequency: AR, US, CA, IN, MY, SG, UK, SE, KE
 Start date: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Stop date: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Duration of therapy: US, CA, IN, SG, SE, SA
 Indication: AR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Medication bought site: SE
 Product available for testing: SA

Adverse drug reactions details

Date of reactions: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Time of onset: MY, SA
 Description of ADRs: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Recovery date: IN, SG, UK, SE
 Duration of reaction: AR
 Product use error: US
 Product quality problem: US, SA
 Seriousness: AU, IN, MY, SG, UK, SE
 Severity: NZ, MY, KE
 Outcome: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Action taken: KE

Contd

Contd

Table 1: Comparative evaluation of ADRs forms of 13 countries**Parameters Countries Following****Possible cause: SE**

Causality: IN, MY, SG, SE, KE
 Effect on daily life: SE
 Effect of drug withdrawal: US, CA, IN, MY, SE
 Rechallenge: AR, NZ, US, CA, IN, MY, SG, UK, SE, SA
 Treatment: AR, AU, CA, MY, SG, SE, KE, SA
 Pt. hospitalized or not: MY, SG, SE
 Date of death: MY, SG

Concomitant drug details

Drug: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Batch no.: MY, SG, UK
 Start date : BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Stop date: AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Route of administration: NZ, CA, MY, SG, UK, KE, SA
 Dose: AU, NZ, CA, MY, SG, UK, KE, SA
 Frequency: AU, CA, MY, SG, UK, KE
 Indication: AU, NZ, MY, SG, UK, SE, KE, SA

Reporter details

Name: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Address: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Occupation: AR, US, CA, IN, MY, SG, SE, KE
 Specialty: IN, UK, SA
 Phone no./mail I.D.: AR, BR, AU, NZ, US, CA, IN, MY, SG, UK, SE, KE, SA
 Date of report: AR, AU, NZ, US, CA, IN, UK, SE, KE, SA
 Any health professional: AU, US, CA
 Reported to health professionals: US, CA, SE
 Signature: AU, NZ, US, CA, IN, UK, SE, KE, SA
 Additional information free text: AR, AU, US, MY, SG, UK, SE, KE, SA

AR: Argentina, BR-Brazil, AU: Australia, NZ: New Zealand, US: United States, CA: Canada, IN: India, MY: Malaysia, SG: Singapore, SE: Sweden, KE: Kenya, SA: South Africa.

name, its dose, route of administration, frequency, start date, stop date, and its indication correlates reported ADR and suspected drug. Similarly concomitant drug details (such as name of drug, route, dose, frequency, start, stop date, and indication) determine whether ADR is due to suspected drug or due to drug-drug interaction, which stands as a common cause in the present poly-pharmacy practice. These data elements relate whether the ADR is solely due to pharmacological property of the suspected drug or due to incorrect dose or frequency of suspected or concomitant drug. In that case, the information classifies the reported ADR as medication error, which is not an ADR, but is another type of drug related problem.

Dechallenge and rechallenge are essential information which assess causality. On analyzing the forms, dechallenge information is reported only in USA, Canada, India, Malaysia, and Sweden while rechallenge information is reported in Argentina, New Zealand, USA, UK, Canada, India, Malaysia,

Table 2: Proposed generic ADR reporting form

Institution details								
Name of institution/Institution code:								
Address:								
Contact no:								
Patients details:								
Patient name:								
Identification no:								
Gender: Male/Female								
Age:								
Date of birth:								
Weight:								
Height:								
Ethnicity:								
Patient's additional information:								
Diagnosis:								
Allergy: ☐ No ☐ Yes (specify)								
Pregnancy status:								
Medical history (if any known):								
Habits: ☐ Smoking ☐ Alcohol ☐ Tobacco ☐ Any other								
Lab investigation:								
Renal/Hepatic dysfunction:								
Adverse drug reaction details:								
Adverse reaction description: _____								
Date of onset:								
Onset time (if known):								
Recovery date (if recovered):								
Dechallenge: ☐ No ☐ Yes								
Rechallenge: ☐ No ☐ Yes ☐ Unknown								
Action taken: ☐ Withdrawal suspected drug ☐ Reduced dose ☐ No change ☐ Unknown treatment: ☐ Specific (mention) ☐ Symptomatic ☐ Nil								
Unknown Causality: ☐ Certain ☐ Probable/Likely								
Possible/Unlikely Conditional/Unclassified								
Unassessable/Unclassifiable severity:								
Mild								
Moderate								
Severe								
Fatal (mention date of death) ☐ Unknown seriousness								
Death								
Life threatening ☐ Hospitalization/prolonged hospitalization ☐ Disability ☐ Congenital anomaly/birth defect Outcome:								
Recovered ☐ Not yet recovered ☐ Fatal ☐ Unknown								
Suspected drug details:								
Dosage	Drug name	Dose	Route of administration	Frequency	Start date	Stop date	Indication	Product Manufacturer Name/Batch Number/Registration Number of Manufacturer (If Known)
Concomitant Medication:								
Drug name	Dose	Route of administration	Frequency	Start date	Stop date	Indication		
Additional Information – Free Text _____								
Reporter Details:								
Name of Reporter:				Profession:				
Phone No/Mail I.D.:				Date of report:				Signature:

Singapore, Sweden, and South Africa. ADR details such as severity and seriousness distinguish ADR-related intensity and outcome.^[19]

Product manufacturer's name, batch number, registration number of the manufacturer help to trace the problem if associated with a particular batch of the drug. The last section of an ADR form should have reporter and institution details, which authenticates the report. On evaluation, it was found that reporter details are present in all 13 ADR forms; however, only Kenya and Malaysia ADR forms contained institution details.

Considering the existing variability in ADR forms, the proposed generic ADR form is comprehensively designed to report information for correct causality assessment [Table 2].

CONCLUSION

The study and evaluation of 13 different forms of various countries representing each geographical region destines the need of a single, concise, self-sufficient, and informative ADR form. The designed ADR reporting format consists of 58 requisite elements which are imperative for inferring an authentic causality assessment. This draft could serve as a basis to develop a uniform ADR reporting system globally.

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