Potential Ways to Enhance ADR Reporting Given Current Concerns

In previous commentaries, we discussed potential ways to enhance the quality and efficiency of medicine use amongst all key stakeholder groups and across health-care sectors.[1,2] We would now like to focus on adverse drug reactions (ADRs), which can be defined as harmful or unpleasant unintended reactions, resulting from the use of medicines occurring at doses normally used in man.[3,4] Adverse drug events (ADEs) are now commonly used as a wider term than ADRs, defined as an injury resulting from the use of a medicine; however, not necessarily causally related to that medicine.[3,5,6] ADEs incorporate a number of areas including ADRs, drug allergies, medication errors, and overdoses.[3,6]

No medicine is without an ADE.[7] However, the limitations of clinical trials, including the careful selection of patients, make it extremely difficult to identify and predict all potential ADEs in subsequent clinical practice.[6,8,9] This is especially important if the patients in routine clinical care are more elderly and with greater comorbidities than those patients recruited into clinical trials.[8,10] In addition, where there can be different patient populations between those enrolled into the clinical trials and those routinely seen in clinical practice. One disease area is patients with human immunodeficiency virus (HIV), where there can be appreciable differences in the profile of patients in sub-Saharan Africa versus other countries including high-income countries.[11,12] Overall, there is an appreciable proportion of women with HIV in sub-Saharan Africa including those with comorbidities such as the metabolic syndrome and diabetes, which will make a difference with potential ADEs reported in clinical trials for new HIV medicines if these are predominantly conducted in countries and regions with a low proportion of women with HIV, a high proportion of intravenous drug users, and low levels of comorbidities.[3,12-14] We are aware anyway that generally more ADRs are reported from women; however, a higher proportion of serious and fatal ADRs are seen amongst reports from males.[15] In addition, there can be concerns with underreporting of ADRs in clinical trials.[9] Consequently, it is important to collect ADE data from other sources.

ADEs and ADRs have appreciable economic consequences as they can result in increased hospitalisations, morbidity, mortality and costs.[16-20] Consequently, identifying ADEs is important to all key stakeholder groups. ADE information can subsequently be built into future quality improvement programmes and prescribing support systems. This includes warning physicians about potential drug: drug interactions that are not seen in the clinical trials, and subsequently avoiding these, as well as introducing procedures to switch therapies early if needed once ADEs appear.[21] According to the World Health Organization (WHO), approximately 10%–80% of all ADEs can be prevented.[22] Alongside this, health-care professionals (HCPs) can warn patients of potential ADEs they could experience during consultations and not necessarily be afraid of these. This is important because adherence to medicines is known to be suboptimal, especially in patients with chronic noncommunicable diseases, and experiencing unknown side effects can potentially aggravate the situation.[15,23-25]

Spontaneously reported ADEs has become one of the most effective interventions designed to collect data concerning safety issues of new medicines in clinical care after their authorization for use by regulatory authorities.[3,26] This approach is able to provide voluminous data at the lowest cost.[3,27-29] Spontaneous reporting is a system whereby case reports of ADEs are voluntarily submitted by HCPs and pharmaceutical company manufacturers to national regulatory authorities.[6]

The WHO since 1970 has introduced numerous drug safety monitoring activities across countries to improve ADE reporting. This includes the establishment of the WHO Programme for International Drug Monitoring (PIDM) and a Collaborating Centre in Sweden, also known as the Uppsala Monitoring Centre (UMC). The joint efforts of this collaboration has resulted in the establishment of the global WHO database known as VigiBase®, which facilitates the exchange of safety information and the provision of guidelines on monitoring drug safety.[6] Recent activities include documenting ADRs associated with remdesivir, particularly in patients with COVID-19, to help guide future care.[30] The WHO PIDM comprises a network of national pharmacovigilance centres (NPCs) that operate independently and whose activities are coordinated and facilitated by the WHO and UMC. The crucial role of the UMC in this global pharmacovigilance system is to manage the global WHO database with reports sent to it by the NPCs as well as use the database to detect

new adverse reaction signals and communicate these back to the NPCs for decisions. The core functions of the NPCs are to collect and collate suspected ADRs reported to them, assess the case reports to determine the quality of documentation, causality and clinical relevance, as well as identify signals with the help of the UMC.[3,6] Subsequently, communicate relevant safety information to national, regional and local regulatory authorities, HCPs, pharmaceutical companies and policymakers. At least 153 countries have now implemented spontaneous reporting systems according to the WHO PIDM,[6] and this number is growing. Spontaneous reports depend mainly on the voluntary reporting by HCPs including physicians, pharmacists and nurses as well as through patients/consumers. For non-prescription medicines, reports received from consumers may provide the only source of signals.

However, spontaneous reporting is plagued by appreciable underreporting across countries.[3,31-34] It is estimated that only 5%–10% of ADRs are reported.[35,36] This needs to be addressed as underreporting of ADRs delays alert signals and has a negative influence on public health. Identified barriers to ADE reporting by HCPs include fear of litigation, poor knowledge on what and how to report ADRs, indifference, unavailability of reporting forms and lack of time to complete the necessary forms.[33-35,37-40]

Numerous interventions have been instigated by different NPCs to improve ADE reporting, especially by HCPs and patients. Some of the known HCPs-oriented interventions include educational activities, simplification of reporting forms, modification of reporting procedures including the introduction of electronic tools, incentivizing HCPs with the provision of continuous professional education credits and financial rewards as well as increasing feedback to ADE reporters.[6,41-45] A systematic review by Paudyal *et al.* reported a 3.5-fold increase in reporting by HCPs when a combination of financial and face-to-face educational interventions were employed. However, there were concerns with the quality of most published studies.[45] Another systematic review reported a 10-fold increase in ADE reporting following a combination of educational interventions and reminders amongst physicians and an approximately 6-fold increase amongst pharmacists.[6] The reporting rates appreciably improved further when a financial reward was made available, i.e., up to as 50-fold increase in reporting rates.[6] Ribeiro-Vaz *et al.*(2012 and 2016) also saw reporting rates increase with a variety of approaches including educational approaches and hyperlinks.[31,46]

Direct reporting of ADE by patients to NPCs has been recognised as one way of reducing underreporting rates; however, there are concerns with the extent of underreporting as well amongst patients.[7,35,47,48] Patients who are knowledgeable about their health conditions and treatments can help improve drug safety by reporting ADRs directly to the NPC, and these reports can be in more detail that those supplied by HCPs.[48,49] Identified barriers to ADR reporting by patients included mailing costs, lack of feedback on previously ADR submitted, difficulties with ADR reporting procedures and forms, inability to recall the names of pertinent medicines as well as confusion regarding whom to report ADRs to.[50,51] These barriers share similarities with those reported by HCPs; consequently, can potentially be addressed through similar approaches.[51-53] Specific interventions known to improve ADR reporting by patients include the promotion of ADR consumer reporting schemes, removing barriers to mailing costs and addressing current challenges.[36,45]

In conclusion, we have documented the impact of ADEs on morbidity, mortality and costs. We have also reported this, the considerable underreporting of ADEs by HCPs and patients, and the potential rationale for this. Such activities have considerable impact on all key stakeholders in the future. Consequently, it is imperative that countries seek to enhance their ADE reporting by HCPs and patients to the benefit of all. We will continue to monitor this.

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Submitted: 19-03-2021 **Revised:** 19-03-2021
Accepted: 19-03-2021 **Published:** 14-05-2021

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DOI: 10.4103/aihb.aihb_41_21

How to cite this article: Sefah IA, Godman B. Potential ways to enhance ADR reporting given current concerns. Adv Hum Biol 2021;11:137-40.