

EDITORIAL

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“Implementing novel pharmacovigilance programs, which augment existing FDA efforts, could improve the detection of safety signals – potentially saving countless lives.”

¹South Carolina College of Pharmacy, Columbia, SC, USA

²Hollings Cancer Center of the Medical University of South Carolina, Columbia, SC, USA

³William Jennings Bryan Veterans Administration Medical Center, Columbia, SC, USA

⁴Arnold School of Public Health of the University of South Carolina, Columbia, SC, USA

*Author for correspondence:

Tel.: +1 803 777 9004

Fax: +1 803 777 2820

E-mail: bennettc@sccp.sc.edu

Attention must be paid: adverse event reporting needs improvement

Samuel J Kessler¹ & Charles L Bennett^{*1,2,3,4}

The insightful review by Russell and Colevas discusses various tools used in the reporting of adverse events, highlighting the need for consistent adverse event reporting guidelines [1]. With clinical trial data being larger and more complex than ever, accurate toxicity reporting is necessary to assess a drug's efficacy and safety profile – the two factors that serve as an integral base for regulatory decision making. Both in and out of clinical trial settings, reporting rates are low and adverse event reports are often incomplete. To date there is no standard approach for adverse event reporting. The Common Terminology Criteria for Adverse Events (CTCAE) serves as a lexicon used to define an adverse event and its severity. In clinical trials, reports are graded in terms of the CTCAE v4.0 terminology – this system uses definitions from the Medical Dictionary for Regulatory Activities (MedDRA). To improve medication safety initiatives, established reporting guidelines are needed.

In oncology trials, adverse events may arise from iatrogenic causes or from an underlying disease. The CTCAE v4.0 defines an adverse event as “any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medical treatment or procedure.” Adverse events can be symptoms, exam finding, abnormal laboratory values, or irregular radiology reports. A serious adverse event is life threatening, requires hospitalization, results in disability, or results in an abnormality or birth defect.

In the CTCAE v4.0, adverse events are organized into System Organ Classes. These groups are based on anatomical, physiological or etiological criteria and are easily mapable to the MedDRA. The terminology was agreed upon by the National Cancer Institute and the European Medicines Agency. The severity of the adverse event is ranked on a 1–5 scale; one being the least severe and five resulting in death. This scale is not included in the MedDRA definitions – as it is unique to the CTCAE. Adverse event categories cover a wide array of laboratory values and clinical findings.

Russell *et al.* examine adverse event reporting in clinical trials and provided eight recommendations for clinical investigators [1]:

- Collect all serious adverse events without regard to causality;
- Collect only intervention-associated low-grade adverse events;
- Specify in advance the subset of trial-specific adverse events of high priority;
- Develop a systematic tool to investigate high-priority adverse events;
- High-priority adverse event tools should use patient-reported outcomes for nonanalytical adverse events;
- Collect adverse events at baseline with every treatment cycle and after treatment completion;

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- Ensure there is a plan for determining recurrent from persistent high-grade adverse events;
- Ensure all adverse event data collected are reported consistently in the literature and to regulatory authorities.

If these recommendations were followed, data extracted from clinical trials would be stronger. Furthermore, trial parameters would be more sensitive to unpredictable events that may occur. Improving adverse event reporting protocols would improve safety monitoring in both clinical trial settings and in the context of clinical practice. Current pharmacovigilance efforts are hindered by two major factors: the underreporting of adverse events and the incompleteness of adverse event reports.

Many significant adverse events go through clinical trial networks undetected. As of 2005, only half of the newly discovered serious adverse drug reactions were detected and documented within 7 years of drug approval [2]. Moore, Singh and Furberg estimate that it takes a median of 11 years to identify a serious adverse drug reaction and to disseminate the information to the appropriate parties. Many drugs with unknown and unfavorable toxicity profiles enter the market and are prescribed to thousands of patients before these events are identified [3]. A Southern Network on Adverse Reactions review looked at US FDA action surrounding three adverse drug reactions; it took 81 years to identify aspirin-associated Reye's syndrome, 13 years to detect erythropoietin-associated pure red cell aplasia and 17 years to detect gadodiamide-associated nephrogenic systemic fibrosis [4].

Underreporting estimates are considerably lower outside of the context of a clinical trial. Another Southern Network on Adverse Reactions study examined underreporting of hemorrhagic and thrombotic events associated with warfarin, clopidogrel and ticlopidine. These three agents were chosen due to the great diversity between them. Of 33,171 warfarin-associated hospitalizations and 67,200 hemorrhage cases, a reporting rate of 1.07 and 1.02% was calculated (for patients aged 65 or older), respectively. Of 13,363 hospitalizations associated with clopidogrel and ticlopidine, a 0.9% reporting rate was calculated. The 9-year reporting rate for venous thromboembolism associated with thalidomide was calculated to be 2.3%.

The usefulness of adverse event reports depends on the content presented in these reports. In the context of clinical trial reporting, Institutional Review Board databases are often lacking completeness. Dorr *et al.* reviewed several clinical trials of imatinib, comparing the quality of clinically documented significant adverse event reports to those reported to the institutional review

board (IRB) [5]. Significant adverse event descriptions were more complete (95 vs 40.3%) in the primary clinical data versus reports from the IRB [5]. Causality was assigned in 93% of the primary clinical data versus 26% in IRB reports [5]. Incompleteness was also observed in the CONSORT system. Péron *et al.* investigated adherence to the CONSORT system during cancer therapy [6]. Reporting trends were analyzed for 325 random clinical trials and an adverse event reporting quality score was assigned. The mean adverse event reporting quality score was 10.1 using a 16-point scale. Most poorly rated were adverse event collection methodology (adequately reported in 10% of studies), description of adverse event characteristics (15%) and attribution to iatrogenic causes (38%) [7].

A complete adverse event report should be thorough, including enough information so that a third party is able to pick up the report and understand the details of the event. To ensure completeness of adverse event reports we recommend that the following be the minimum included information:

- Patient information: age, gender, weight, country or region;
- Drug information: drug name, indication (diagnosis for use), dose, manufacturer, frequency and route of administration, therapy dates, other medical products/therapies, whether the event abated after use stopped and whether the event reappeared after reintroduction;
- Event description: outcome attributed to adverse event, date of event, date of report, description of event, relevant tests/laboratory data, patient history and treatment of event;
- Other: report source, type of report, and agencies receiving report.

Adverse event reporting both inside and outside of clinical trial settings is essential for medication safety initiatives. The pitfalls of our current system lie in its lack of protocol and its voluntary nature. With wide implementation and clear-cut protocols, adverse event monitoring systems would be able to pick up novel events in a more efficient manner.

Complete reporting of adverse events can be time consuming. As it is, healthcare professionals are overburdened by paperwork. Reporting of adverse events should be tailored to maximize efficiency of reporting, whilst minimizing the burden of extra paperwork.

There might be an opportunity for a call center that could provide feedback and evaluation to patients and providers who may have observed an adverse drug reaction. The call center would be modeled on poison control centers. The operators at the center would be

trained to potentially detect additional information from the healthcare professionals who witnessed the adverse events. Adverse events would be entered into a database by the call center staff. Furthermore, the operators would be able to assist healthcare practitioners and patients by providing clinically relevant adverse event data. The data would also be transmitted to the FDA.

The current paradigm for adverse event reporting needs improvement. As it is, the initiation of a report and the content held within the report are decided either by the individual healthcare professional or through institutional policy. Current reporting rates in clinical trials remain below IRB protocol. Outside of trial settings no reporting mandates exist, therefore, the nonreporting rates remain even higher. Establishing universally accepted protocol and implementing new routes of reporting and dissemination have the

potential to increase both reporting rates and report quality. Implementing novel pharmacovigilance programs, which augment existing FDA efforts, could improve the detection of safety signals – potentially saving countless lives.

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