trials are often small and of limited duration, and the patients in clinical trials are healthier than unselected patients in routine clinical practice. Thus, the public and physicians rely on the US Food and Drug Administration (FDA) Adverse Event Reporting System to inform us of unknown or unsuspected risks associated with use of drugs and devices.

In this issue of *JAMA Internal Medicine*, Ma and colleagues\(^1\) reviewed almost 1.27 million AE reports submitted in a 10-year period and found that approximately 10% of these reports, including more than 40 000 reports of patient deaths, were not received by the FDA within the required 15-day time frame for reporting serious AEs. Such reporting delays should never occur, as they mean that more patients are exposed to potentially avoidable serious harm, including death. However, no disciplinary actions have been taken when companies fail to submit reports to the FDA in the time frame required. Clearly, the lack of consequences contributes to a lack of deterrence for these illegal and dangerous delays.

There is another enforcement tool that the FDA could begin to deploy immediately: suspending drug sales or withdrawing drug approval. Federal regulations give the FDA the power to withdraw drug approval if an applicant fails to establish and maintain records and make [timely] reports as required under this section....\(^\text{2}\) One improvement would be for AE reports to go directly to the FDA instead of via the manufacturer, as recommended by Ma et al. This would address the delay problem, although additional efforts to make the data available and take appropriate actions are still necessary. Physicians and their patients must be knowledgeable of benefits, harms, and alternatives for a wide choice of treatments, especially those recently approved for which clinical experience is limited.

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Conflict of Interest Disclosures: None reported.  
Correction: This article was corrected for a typographical error in the second paragraph on July 27, 2015.


Disclosure of Boxed Warnings to Research Participants

Medical experimentation on human subjects may involve drugs already approved for marketing by the US Food and Drug Administration (FDA). About 35% of FDA-approved drugs carry a boxed warning in the manufacturer’s full prescribing information,\(^1\) usually because of a potential toxic effect “so serious in proportion to the potential benefit from the drug (eg, a fatal, life-threatening, or permanently disabling adverse reaction) that it is essential that it be considered in assessing the risks and benefits of using the drug.”\(^2\) The consent form both documents and facilitates the process for negotiation of consent between the study participant and investigator. Here, we assess adequacy of disclosure of boxed warning risks to study participants on consent forms.

Methods | Using an electronic database of institutional review board (IRB) records, we identified 4780 human biomedical research protocols active between January 1, 2010, and December 31, 2012, at a single academic medical center, identifying each protocol that had contemporaneous boxed warnings. Study type was classified as industry sponsored, government agency sponsored, or nonsponsored. Statistical calculations were made using exact probabilities.\(^3\) For each consent form, 2 researchers (S.M.B. and P.L., each a board-certified internist) independently assessed disclosure of relevant boxed warning risks. Reviewer discrepancies were resolved under independent review by 2 research team members (E.M.Y. and a pharmacologist-pharmacist) with extensive senior-management level IRB experience. The study was conducted from February 4, 2012, to May 15, 2015. The Northwestern University Institutional Review Board granted approval for this study.

Results | We identified 44 boxed warning risks applicable to 57 protocols (1.2% of all human research protocols) that involved 17 study drugs (Table). Of the 57 protocols, 43 (75%) involved participants with life-threatening diseases. Of the corresponding 57 consent forms, 36 (63%) did not disclose boxed warning risks. All sponsored research protocols in this study were for multicenter studies. The rate of non-disclosure of 1 or more boxed warning risks in a consent form was 17 of 21 (81%) for nonsponsored research, 9 of 16 (56%) for industry-sponsored research, and 10 of 20 (50%) for government agency-sponsored research. The nondisclosure rate for nonsponsored research was significantly higher than for government agency-sponsored research ($P < .05$); differences among other pairs were not statistically significant ($P > .16$).

Discussion | We found that for protocols involving drugs with boxed warnings, 63% of consent forms did not disclose 1 or more boxed warning risks. The higher nondisclosure rate of boxed warnings in nonsponsored research compared with government agency-sponsored research may reflect procedural variability, as sponsored research projects typically involve multiple levels of internal and external review.

Investigators and sponsors have access to more information about risk of harm than do patients and study participants. Sponsors and investigators have inherent conflicts of interest, as clinical trials may generate income or enhance reputation. Moreover, some investigators are clinicians providing routine medical care to study participants who are also their patients. Adequacy of informed consent is of particular concern with vulnerable, gravely ill patients who participate in clinical trials.\(^4\)
The IRB’s role includes mitigation of misaligned motives, blurred roles, and asymmetries in information and power. Our finding that some serious risks in boxed warnings are undisclosed in consent forms is an important issue ipso facto, and as potential study participants may be disinclined to participate if they fear that there may be undisclosed risks.

Our finding that 19 of the 36 sponsored multicenter studies did not disclose boxed warning risks in the consent forms suggests that this problem may be a pervasive issue. There is a pressing need for timely and accurate communication from the manufacturer to the investigator to the IRB and to study participants about serious and/or life-threatening risks as conveyed in the FDA-mandated boxed warning. Semi-automated analysis of consent forms, protocols, investigator brochures, the manufacturer’s full prescribing information, and other documents may assist verification of disclosure of risks to study participants.

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Conflict of Interest Disclosures: None reported.

Additional Contributions: Dennis P. West, PhD, Department of Dermatology, Northwestern University Feinberg School of Medicine, contributed to the design, conduct, and supervision of this study and analysis of the data, and assisted in writing and editing the manuscript. Paul Yarnold, PhD, Optimal Data Analysis LLC, contributed to the statistical analysis of the data and reviewed the manuscript. Beatrice Nardone, MD, PhD, Department of Dermatology, Northwestern University Feinberg School of Medicine, contributed to the design and conduct of this study and analysis of the data, and reviewed the manuscript. None of the contributors were compensated for their contributions.


