Guidance for Clinical Investigators, Sponsors, and IRBs

Adverse Event Reporting to IRBs — Improving Human Subject Protection

U.S. Department of Health and Human Services
Food and Drug Administration
Office of the Commissioner (OC)
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
Good Clinical Practice Program (GCPP)

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Contains Nonbinding Recommendations

Guidance for Clinical Investigators, Sponsors, and IRBs[1] Adverse Event Reporting to IRBs — Improving Human Subject Protection

This guidance represents the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist the research community in interpreting requirements for submitting reports of *unanticipated problems*, including certain adverse events reports, to the institutional review board (IRB) under Title 21 of the Code of Federal Regulations (21 CFR) part 56 (Institutional Review Boards), part 312 (Investigational New Drug Application), and part 812 (Investigational Device Exemptions). Specifically, the guidance provides recommendations for sponsors and investigators conducting investigational new drug (IND) trials to help them differentiate between those adverse events that are unanticipated problems that must be reported to an IRB and those that are not. The guidance also makes suggestions about how to make communicating adverse events information to IRBs more efficient.

FDA developed this guidance in response to concerns raised by the IRB community, including concerns raised at a March 2005 public hearing,[2] that increasingly large volumes of individual adverse event reports submitted to IRBs—often lacking in context and detail—are inhibiting, rather than enhancing, the ability of IRBs to protect human subjects.

FDA regulations use different terms when referring to an *adverse event*. For example, *adverse effect* is used in 21 CFR 312.64; *adverse experience* is used in § 312.32; and *unanticipated problems* is used in § 312.66. For the purposes of this guidance, the term *adverse event* is used, except when quoting specific regulations. For device studies, part 812 uses the term *unanticipated adverse device effect*, which is defined in 21 CFR 812.3(s).

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should

[1] This guidance has been prepared by the Office of the Commissioner, the Center for Drug Evaluation and Research (CDER), the Center for Biologics Evaluation and Research (CBER), the Center for Devices and Radiological Health (CDRH), and the Good Clinical Practice Program (GCPP) at the Food and Drug Administration.

[2] *Federal Register,* "Reporting of Adverse Events to Institutional Review Boards; Public Hearing," (70 FR 6693, March 21, 2005).

be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

FDA regulates clinical studies authorized under sections 505(i) (drugs and biologics) and 520(g) (devices) of the Federal Food, Drug, and Cosmetic Act. All such clinical studies must be reviewed and approved by an IRB before the study is initiated, in accordance with the requirements of 21 CFR part 50 (Protection of Human Subjects), part 56 (Institutional Review Boards), and either part 312 (Investigational New Drug Application) or part 812 (Investigational Device Exemptions) (see §§ 50.1, 56.101, 312.23(a)(1)(iv), 312.40(a), 812.2(b)(1)(ii), 812.2(c) and 812.62(a)).[3] After the initial review and approval of a clinical study, an IRB must conduct continuing review of the study at intervals appropriate to the degree of risk presented by the study, but at least annually (§ 56.109(f)). The primary purpose of both initial and continuing review of the study is "to assure the protection of the rights and welfare of the human subjects" (§ 56.102(g)). To fulfill its obligations during the conduct of a clinical study, an IRB must have, among other things, information concerning unanticipated problems involving risk to human subjects in the study, including adverse events (AEs) that are considered unanticipated problems (§§ 56.108(a)(3), (4), (b)).[4]

For clinical investigations of drug and biological products conducted under an investigational new drug (IND) application, information about adverse events[5] must be communicated among investigators, sponsors, and IRBs as follows:

- Investigators are required to report promptly "to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (§ 312.64(b)).
- Sponsors are specifically required to notify all participating investigators (and FDA) in a written IND safety report of "any adverse experience associated with the use of the drug that is both serious and unexpected" and "any finding from tests in laboratory animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)). And, more generally, sponsors are required to "keep each participating investigator informed of new observations discovered by or reported to the sponsor on the drug, particularly with respect to adverse effects and safe use" (§ 312.55(b)).

[3] As described below, there are some differences between the requirements for investigational new drug and investigational device exemption studies, as they concern obligations to report to a reviewing IRB.
[4] Unanticipated problems may be adverse events or other types of problems, i.e., adverse events are a subset of unanticipated problems.
[5] The IND regulations use the term *adverse effect* (§ 312.64) and *adverse experience* (§ 312.32). These terms are interchangeable with *adverse event*.

- Investigators are required to report promptly "to the IRB… all *unanticipated problems* involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

A critical question for studies conducted under part 312 is what adverse events ***should*** be considered *unanticipated problems* that merit reporting to an IRB. In the years since the IRB and IND regulations issued, changes in the conduct of clinical trials (e.g., increased use of multi-center studies, international trials) have complicated the reporting pathways for adverse event information described in the regulations. In particular, the practice of local investigators reporting individual, unanalyzed events to IRBs, including reports of events from other study sites that the investigator receives from the sponsor of a multi-center study—often with limited information and no explanation of how the event represents an unanticipated problem—has led to the submission of large numbers of reports to IRBs that are uninformative. IRBs have expressed concern that the way in which investigators and sponsors of IND studies typically interpret the regulatory requirement to inform IRBs of all "unanticipated problems" does not yield information about adverse events that is useful to IRBs and thus hinders their ability to ensure the protection of human subjects. This guidance is intended to help differentiate those adverse events that should be considered unanticipated problems (and thus reported to the IRB) from those that should not, thereby helping to ease the burden on IRBs and make the adverse events information they receive more informative and useful.

III. REPORTING AEs TO IRBs IN CLINICAL TRIALS OF DRUG AND BIOLOGICAL PRODUCTS CONDUCTED UNDER IND REGULATIONS

A. How to Determine If an AE is an Unanticipated Problem that Needs to Be Reported

In general, an AE observed during the conduct of a study should be considered an unanticipated problem involving risk to human subjects, and reported to the IRB, ***only*** if it were unexpected, serious, and would have implications for the conduct of the study (e.g., requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure). An individual AE occurrence ***ordinarily*** does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

Many types of AEs generally require an evaluation of their relevance and significance to the study, including an aggregate analysis of other occurrences of the same (or similar) event, before they can be determined to be an unanticipated problem involving risk to human subjects. For example, an aggregate analysis of a series of AEs that are commonly associated with the underlying disease process that the study intervention is intended to treat (e.g., deaths in a cancer trial), or that are otherwise common in the study population independent of drug exposure (e.g., cardiovascular events in an elderly population) may reveal that the event rate is higher in the drug treatment group compared to the control arm. In this case, the AE would be considered an unanticipated problem. In the absence of such a finding, the event is uninterpretable.

The major exceptions to the general rule that an isolated event is not informative are serious AEs that are uncommon and strongly associated with drug exposure, such as angioedema, agranulocytosis, anaphylaxis, hepatic injury, or Stevens Johnson syndrome. In most cases, a single, unexpected occurrence of this type of event would be considered an unanticipated problem involving risk to human subjects and, thus, must be reported to the IRB. Similarly, one or a small number of serious events that are not commonly associated with drug exposure, but are otherwise uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy) should be considered an unanticipated problem involving risk to human subjects.

Because they have been previously observed with a drug, the AEs listed in the investigator's brochure would, by definition,[6] not be considered unexpected and thus would not be unanticipated problems. Possible exceptions would include situations in which the specificity or severity of the event is not consistent with the description in the investigator's brochure, or it can be determined that the observed rate of occurrence for a serious, expected AE in the clinical trial represents a clinically important increase in the expected rate of occurrence.

Therefore, FDA recommends that there be careful consideration of whether an AE is an unanticipated problem that must be reported to IRBs. In summary, FDA believes that only the following AEs should be considered as *unanticipated problems* that must be reported to the IRB.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).
- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.
- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an

[6] An unexpected adverse drug experience is defined as "[a]ny adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. *Unexpected*, as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure), rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product." (21 CFR 312.32(a))

unanticipated problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.

- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). We recommend that a discussion of the divergence from the expected rate accompany the report.
- Any other AE or safety finding (e.g., based on animal or epidemiologic data) that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the IRB to ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

B. How to Report Unanticipated Problems to IRBs

In a multicenter study, it is clear that individual investigators must rely on the sponsor to provide them information about AEs occurring at other study sites. It is also clear that the sponsor receives AE information from all study sites and typically has more experience and expertise with the study drug than an investigator. Accordingly, the sponsor is in a better position to process and analyze the significance of AE information from multiple sites and—when the determination relies on information from multiple study sites or other information not readily accessible to the individual investigators (e.g., a sponsor's preclinical data that supports the determination)—to make a determination about whether an AE is an unanticipated problem. Furthermore, the regulations require the sponsor of an IND to promptly review all information relevant to the safety of the drug and to consider the significance of the report within the context of other reports (§ 312.32)[7]

The regulations state that for studies conducted under 21 CFR part 312, investigators must report all "unanticipated problems" to the IRB (§§ 312.66, 312.53(c)(1)(vii), and 56.108(b)(1)). However, as discussed above, we recognize that for multicenter studies, the sponsor is in a better position to process and analyze adverse event information for the entire study and to assess whether an adverse event occurrence is both *unanticipated* and a *problem* for the study.

Accordingly, to satisfy the investigator's obligation to notify the IRB of unanticipated problems, an investigator participating in a multicenter study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor. In addition, if the investigator knows that the sponsor has reported the unanticipated problem directly to the IRB, because the investigator, sponsor, and IRB made an explicit agreement for the sponsor to report directly to the IRB,[8] and because the investigator was copied on the report from the

[7] Section 312.32(c)(1)(ii) requires a sponsor preparing an IND safety report to, among other things, "analyze the significance of the adverse experience in light of previous, similar reports." Section 312.32(b) requires the sponsor to "promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source . . . ."

[8] Note that such an agreement would be required to be incorporated into the IRB's written procedures (21 CFR 56.108(b)(1), 56.115(a)(6)).

sponsor to the IRB, FDA intends to exercise its enforcement discretion and would not expect an investigator to provide the IRB with a duplicate copy of the report received from the sponsor.

IV. REPORTING AEs TO IRBs IN CLINICAL TRIALS OF DEVICES UNDER THE IDE REGULATIONS

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.

V. CONCLUSION

The receipt of a large volume of individual AE reports without analysis of their significance to a clinical trial rarely supports an IRB's efforts to ensure human subject protection. Sponsors can assess the implications and significance of AE reports promptly and are required to report serious, unexpected events associated with the use of a drug or device, including analyses of such events, to investigators and to FDA. In addition, sponsors are required to report analyses of unexpected adverse device experiences to IRBs. FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful AE information. The ultimate goal is to provide more meaningful information to IRBs, particularly when sponsor analysis (including an analysis of the significance of the adverse event, with a discussion of previous similar events where appropriate) is made available to IRBs.