Guidance for Clinical Investigators, Sponsors, and IRBs

Adverse Event Reporting — Improving Human Subject Protection

DRAFT GUIDANCE

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Center for Biologics Evaluation and Research (CBER)
Center for Devices and Radiological Health (CDRH)
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Guidance for Clinical Investigators, Sponsors, and IRBs[1] Adverse Event Reporting — Improving Human Subject Protection

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic.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). 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 — often lacking in context and detail — are inhibiting rather than enhancing IRBs' ability to adequately protect human subjects. This guidance provides recommendations to sponsors and investigators for improving the quality of information they provide to IRBs.

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 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

[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).

A. Regulatory Requirements

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 a manner consistent 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) and 812.30(b)(1)).[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 the IRB's obligations to assure the protection of the rights and welfare of human subjects during the conduct of a clinical study, an IRB must have information concerning unanticipated problems in the study and changes in the research activity (§§ 56.108(a)(3), (4), (b)). Such information may be important to the IRB's review.

1. Clinical Investigations of Drugs and Biological Products Under Investigational New Drug (IND) Regulations

Investigators[4] and sponsors[5] have the following regulatory obligations during the conduct of a clinical investigation:

- 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 investigation must report the adverse effect immediately (§ 312.64(b))[6].
- Investigators are required to report promptly to the IRB all *unanticipated problems* involving risks to human subjects or others (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66). A critical question, however, is precisely which occurrences represent such an unanticipated problem.
- 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)).
- Sponsors are specifically required to notify all participating investigators, in a written investigational new drug (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

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[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] Investigator means an individual who actually conducts a clinical investigation (i.e., under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team. 21 CFR 312.3

[5] Sponsor means a person who takes responsibility for and initiates a clinical investigation. 21 CFR 312.3

[6] Typically, the Investigator's Brochure and the protocol identify adverse effects that might reasonably be anticipated in association with exposure to the study drug, and may include a description of the expected frequency of those effects. In addition, consistent with 21 CFR 312.64(b), the protocol usually specifies how adverse event information for identified events, and unexpected events, is to be collected and provided to the sponsor.

animals that suggests a significant risk for human subjects" (§ 312.32(c)(1)(i)(A),(B)). Sponsors are further required to identify in these IND safety reports, all previous safety reports concerning similar adverse experiences and to *analyze the significance of the current adverse experience* in light of the previous reports (§ 312.32(c)(1)(ii)).

In the years since the regulations issued, the increased use of multi-center studies, international trials, and other changes in the conduct of clinical trials have complicated the reporting pathways prescribed in the regulations. In particular, the practice of local investigators reporting individual unanalyzed events to IRBs, including events from all centers in a multi-center study, often with limited information and without any explanation of how the event represents an "unanticipated problem," has led to the submission of large numbers of reports to IRBs that they cannot adequately assess.

2. Clinical Investigations of Devices Under Investigational Device Exemption (IDE) Regulations

- Investigators are required to submit to the reviewing IRB and the sponsor a report of any *unanticipated adverse device effect*[7] (UADE) occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect (§ 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)).

B. IRB Concerns

IRBs have expressed concern that the way in which investigators and sponsors for 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. IRBs note that they receive increasingly large volumes of individual adverse event reports — often lacking in context and detail — that are inhibiting their ability to assure the protection of human subjects. IRBs have informed us that these individual reports are often incomplete and unanalyzed. For example:

- Sponsors may not explain to investigators why an event constitutes an unanticipated problem for a particular study, nor explain how the event relates to the study they are conducting.
- The limited information provided may not allow the IRB to assess the significance of the event.

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[7] An unanticipated adverse device effect is "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)).

- Events that were anticipated to occur (e.g., those that were described in the study protocol, Investigator's Brochure, and informed consent document) are often reported.
- IRBs may receive reports on subjects who have not received the study article (i.e., they are in the control group of the study)
- For events that are part of the underlying disease process or that occur at reasonably large background rates in the subject population (e.g., strokes, heart attacks in an older population), individual reports are almost never informative. Before such events can be determined to be "unanticipated" and the significance of the events can be assessed, a comparison of the incidence of the event in treated and untreated patients is needed.

In summary, given the large volume of individual adverse event reports received, the lack of context and detail in many of the reports, and the great variations in clinical significance of the event(s) described in these reports, IRBs find themselves inundated with information, much of which does not assist them in assuring the protection of the rights and welfare of human subjects. The submission of reports containing incomplete information and inadequate evaluation of the relevance and significance of events, demands IRB attention, but does not allow the IRB to carry out its responsibility to meaningfully evaluate the reports.

C. Part 15 Hearing

In March of 2005, FDA held a public hearing to gather directly from IRBs and other affected parties information about specific problems and concerns related to the reporting of adverse event information to IRBs. FDA also solicited suggestions and recommendations for possible mechanisms to address the problems that were identified. FDA received comments (both written and oral) from a range of parties, including representatives from academic medical center IRBs, commercial IRBs, pharmaceutical and device industry trade organizations, individual pharmaceutical companies, professional organizations representing IRBs, consumer groups, international organizations devoted to bioethics and health policy, and other federal agencies. The comments expressed significant concerns about adverse event reporting to the IRB.

IRBs reported difficulties in reviewing and interpreting the significance of information when large volumes of individual adverse event reports are received in isolation (neither aggregated nor analyzed) at sporadic intervals during the course of a study. In some cases, reports contain insufficient information to assess the significance of an event (e.g., a report may not specify whether the study subject actually received the investigational agent). To address these problems, some IRBs have developed processes (routine or ad hoc) whereby sponsors of multicenter trials voluntarily submit aggregated reports directly to the IRBs. These reports are intended to ensure that the information obtained is interpretable and relevant to the IRB's task of protecting the rights and welfare of human subjects during the conduct of the study. Under these arrangements, some sponsors have provided IRBs with the safety analyses and reports that allow comprehensive assessment of the events, that lead to changes in the protocol, investigator's brochure, or informed consent documents, or that in other ways have clear implications for human subject protection. Such reports are more useful to IRBs than individual reports that are difficult to interpret in isolation. In some cases, IRBs have asked multicenter study sponsors to provide such reports to the investigators, rather than directly to IRBs.

Some comments proposed that investigators should send to IRBs only the following reports of unanticipated problems:

- Summary safety information or analyses of adverse events provided by the sponsor that describe significant changes in a product's safety profile.
- Reports of individual adverse events only if they have significant implications for human subject safety (e.g., a report of acute hepatic necrosis).
- Reports of aggregate data (e.g., analyses and line listings of adverse events) identifying serious unexpected adverse events.
- Reports from a data monitoring committee (DMC), whether these describe concerns or identify no problem.

Some sponsors of multicenter drug trials stated that they are aware of current problems related to the volume and quality of adverse event information submitted to IRBs. They also recognize that by providing IRBs with more meaningful information, sponsors will help IRBs fulfill their obligation to protect the rights and welfare of human subjects. Although sponsors of clinical trials conducted under IND have only limited obligations to provide adverse event information, analyses or summary information directly to IRBs[8], sponsors currently provide this information to investigators and therefore could easily provide it to IRBs.

As previously described in section II.A of this document, unlike sponsors of drug trials, device sponsors have an explicit requirement to conduct an evaluation of an "unanticipated adverse device effect" (UADE) and to present the results of this evaluation directly to the participating IRBs (§ 812.150(b)(1)). At the Part 15 hearing, one commenter noted that this reporting paradigm is an effective mechanism for reducing regulatory burden on the IRBs, while helping to ensure that the data and information they receive is presented in a useful manner.

Some sponsors suggested that sponsors should work with IRBs to help IRBs get the information they need (either directly or through the clinical investigator) to assure the protection of the rights and welfare of human subjects, and that this information should include few individual reports (unless the implications for human subject protection were clear), and more aggregated and summarized data.

III. FDA RECOMMENDATIONS

A. Clinical Investigations of Drugs and Biological Products Under IND

[8] A sponsor who determines that its investigational drug presents an unreasonable and significant risk to subjects must discontinue those investigations that present the risk, and notify all IRBs, investigators, and FDA (21 CFR 312.56(d)).

1. How to Determine if an Adverse Event is an Unanticipated Problem

The requirement that investigators notify IRBs when an "unanticipated problem" occurs is intended to provide IRBs with an alert mechanism when new risks to study subjects come to light. Of course, to be a notifiable occurrence, the event must both be "unanticipated" and represent a "problem" for the study. With few exceptions (e.g., adverse events that are rare in the absence of drug exposure, such as agranulocytosis, hepatic necrosis, Stevens Johnson syndrome), FDA believes that an individual adverse event report cannot be readily concluded to represent an unanticipated problem, even if the event is not addressed in the investigator's brochure, protocol, or informed consent documents. Individual adverse event reports generally require an evaluation of their relevance and significance to the study, including an evaluation of other adverse events, before they can be considered to be an unanticipated problem. FDA believes that reports that lack such evaluation should not be provided to the IRB, since the IRB will be unable to assess the significance of the report for the rights and welfare of human subjects in the study. Reports of unanticipated problems should provide information that is of some relevance to the IRB's responsibility to assure the protection of human subjects (i.e., new information that might affect the IRB's view of the study or that change the study protocol or consent form).

Therefore, FDA recommends that there be careful consideration of whether an adverse event is an unanticipated problem that must be reported to IRBs. All reports to the IRB of unanticipated problems should explain clearly why the event described represents a "problem" for the study and why it is "unanticipated." Sponsors are required to notify investigators of serious and unexpected adverse experiences (§ 312.32(c)(1)(i)(A)), and must keep investigators informed of new observations discovered by or reported to the sponsor, particularly with respect to adverse effects and safe use. (§ 312.55(b)). With regard to the subset of "unanticipated problems" that are also adverse drug experiences, FDA believes that only the following adverse experiences (or events) should be reported to the IRB as "unanticipated problems."

- Any adverse experience that, even without detailed analysis, represents a serious unexpected adverse event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- A series of adverse events that, on analysis, is both unanticipated and a problem for the study. There would be a determination that the series of adverse events represents a signal that the adverse events were not just isolated occurrences and were significant to the rights and welfare of subjects. We recommend that a summary and analyses supporting the conclusion accompany the report.
- An adverse event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, or expected to occur in study subjects at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in subject population), but that occurs at a greater frequency or at greater severity than expected. We recommend that a discussion of the divergence from expected rates accompany the report.

- Any other adverse event 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 assure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

2. How to Report Unanticipated Problems to IRBs

In a multi-center study, it is clear that individual investigators must rely on the sponsor to provide them information about adverse experiences occurring at other study sites. It is also clear that the sponsor, because it receives adverse event information from all study sites and typically has more experience and expertise with the study drug, is in a better position to process and analyze the significance of adverse event information from multiple sites and, therefore, make determinations about whether an adverse event is an unanticipated problem. Further, it is clearly stated in the regulations that it is the responsibility of the sponsor of an IND to undertake the kind of analysis (§ 312.32) that might lead to such a conclusion. Because the sponsor is in a better position to process and analyze information about adverse events across the entire study and is required to conduct analysis of serious and unexpected adverse events, investigators often have to rely on a sponsor's determination whether an adverse event is an "unanticipated problem," to the extent that the determination relies on information from multiple study sites or other information not readily accessible to the investigator (e.g., a sponsor's preclinical data that supports the determination).

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)). 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 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 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,[9] and because the investigator was copied on the report from the 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.

B. For Studies Involving Devices

As discussed in section II.A.2 of this document, the IDE regulations specify which adverse events are UADE for investigational device studies.

[9] 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)).

- 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)).

IV. CONCLUSION

The receipt of a large volume of individual adverse experience reports without analysis of their significance to a clinical trial rarely supports an IRB's efforts to assure human subject protections. Sponsors can assess the implications and significance of adverse experience reports promptly, and are required to report serious unexpected events, including analyses of such events, to investigators and to FDA. FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful adverse event information. FDA believes that implementation of practices such as those recommended in this guidance will 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.