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Adverse Event Reporting To The IRB

Law360, New York (March 11, 2009) -- Institutional Review Boards should review their written policies to determine whether they are consistent with the recommended reporting guidelines described in this new guidance for adverse event information in studies conducted under the investigational new drug regulations.

The U.S. Food and Drug Administration (FDA) regulates certain clinical investigations of drugs and biologics under sections 505(i), and of devices under 520(g), of the Federal Food, Drug and Cosmetic Act.

All such clinical studies must be reviewed and approved by an Institutional Review Board (IRB) prior to study initiation, and they are further subject to the IRB's continuing review at intervals appropriate to the degree of risk presented by the study.

To enable the IRB to fulfill its obligation to assure the protection of human subjects during its continuing review of a clinical study, the 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 (21 CFR Part 56.108(b)(1), Part 312.53(c)(1)(vii), and Part 312.66).

FDA recognizes that the receipt of a large volume of individual adverse event reports without analysis of their significance to a clinical trial rarely supports the IRB's mission to protect human subjects in research.

The FDA guidance published in January 2009 is intended to clarify which subset of adverse events occurring in human subjects participating in research are unanticipated problems and must be reported under 21 CFR Part 56 and Part 312 for FDA-regulated investigations of drug and biological products conducted under an investigational new drug (IND) application.

The FDA believes that for FDA-regulated investigations of devices conducted under the investigational device exemption (IDE), the device regulations under 21 CFR Part 812

already provide clear instructions as to which unanticipated adverse device effect needs to be reported to the IRB.

How to Determine if an Adverse Event Is an Unanticipated Problem that Must Be Reported to an IRB in Studies Under IND Regulations

In general, an adverse event 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 adverse event occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood.

FDA believes that only the following adverse events should be considered unanticipated problems that must be reported to the IRB:

A serious, unexpected event occurs that is uncommon and strongly associated with drug exposure (such as angioedema, agranulocytosis, hepatic injury or Stevens-Johnson syndrome).

A serious, unexpected event occurs singularly, or more often a small number of times, that is not commonly associated with drug exposure, but is uncommon in the study population (for example, tendon rupture or progressive multifocal leukoencephalopathy).

Based on an aggregate analysis of other occurrences of the same (or similar) event, the sponsor of a multi-center study or the investigator of a single site study determines that multiple occurrences of an adverse event is a signal that the adverse events were not just isolated occurrences and involve risk to human subjects (for example, a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control).

A summary and analysis supporting the determination is recommended to accompany the sponsor's or investigator's report to the IRB.

An adverse event occurs that is described or addressed in the investigator's brochure, protocol or informed consent documents, but it occurs at a specificity or severity that is inconsistent with prior observations.

For example, if an elevation in the hepatic enzyme is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects.

A discussion of the divergence from the expected specificity or severity is recommended to accompany the sponsor's or investigator's report to the IRB.

A serious adverse event occurs 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.

A discussion of the divergence from the expected rate of occurrence is recommended to accompany the sponsor's or investigator's report to the IRB.

Any other adverse event or safety finding (for example, based on animal or epidemiological data) occurs 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.

An explanation of the conclusion should accompany the sponsor's or investigator's report to the IRB.

Examples of Adverse Events that Do Not Represent Unanticipated Problems and Do Not Need to Be Reported to an IRB in Studies Under IND Regulations

A subject participating in a phase 3, randomized, double-blind, controlled clinical trial comparing the relative safety and efficacy of a new chemotherapy agent combined with the current standard chemotherapy regimen, versus placebo combined with the current standard chemotherapy regimen, for the management of multiple myeloma develops neutropenia and sepsis. The subject subsequently develops multi-organ failure and dies.

Prolonged bone marrow suppression resulting in neutropenia and risk of life-threatening infections is a known complication of the chemotherapy regimens being tested in this clinical trial, and these risks are described in the IRB approved protocol and informed consent document.

The sponsor and investigators conclude that the subject's infection and death are directly related to the research interventions.

A review of data on all subjects enrolled so far reveals that the incidence of severe neutropenia, infection and death are within the expected frequency. This example is not an unanticipated problem because the occurrence of severe infections and death — in terms of nature, severity and frequency — was expected.

A subject enrolled in a phase 3, randomized, double-blind, placebo-controlled clinical trial evaluating the safety and efficacy of a new investigational anti-inflammatory agent for management of osteoarthritis develops severe abdominal pain and nausea one month after randomization. Subsequent medical evaluation reveals gastric ulcers.

The IRB-approved protocol and informed consent document for the study indicated that there was a 10 percent chance of developing mild to moderate gastritis and a 2 percent chance of developing gastric ulcers for subjects assigned to the active investigational agent.

The sponsor and investigator conclude that the subject's gastric ulcers resulted from the research intervention and withdraw the subject from the study.

A review of data on all subjects enrolled so far reveals that the incidence of gastritis and gastric ulcer are within the expected frequency. This example is not an unanticipated problem because the occurrence of gastric ulcers — in terms of nature, severity and frequency — was expected.

Conclusion

Under current law, FDA requires the sponsors to report meaningful 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 experience to the IRBs for device studies under the IDE regulations. For studies conducted under the IND regulations, FDA requires the investigators to report all “unanticipated problems” to the IRB.

However, in its January 2009 guidance, FDA recognizes that the sponsor of a multicenter IND study is in a better position than any local investigator of a single site to assess the implication and significance of adverse event reports based on its experience and expertise in the products being tested, and adverse event information it receives from all study sites.

Accordingly, FDA encourages the sponsors of a multicenter IND study to report the unanticipated problems in IND investigations directly to a local site's IRB.

Alternatively, an investigator participating in a multicenter IND study may rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor.

All IRBs should review their current written policies and procedures to determine whether they are consistent with the recommended reporting guidelines and pathways described in this new guidance for adverse event information in studies conducted under the IND regulations.

Health care providers, investigators and IRBs should also be cognizant of any applicable state and local laws and regulations, specific federal funding agencies' (for example, the National Institute of Health) policy requirements related to unanticipated

problems and adverse events experienced by research subjects, and international requirements for research conducted outside the United States.

Investigators and IRBs should consult with their legal advisors for guidance regarding pertinent federal, state, local and international laws, regulations and policy requirements regarding the reporting of unanticipated problems and adverse events in human subject research.

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