FDA Issues Final Guidance on Adverse Event Reporting

On January 14, 2009, the US Food and Drug Administration (FDA) released final guidance on the agency's requirement that certain "unanticipated problems" in FDA-regulated clinical trials be reported to an Institutional Review Board (IRB). "Guidance for Clinical Investigators, Sponsors, and IRBs: Adverse Event Reporting to IRBs–Improving Human Subject Protection" responds to concerns expressed by IRBs about the increasing volume of adverse event reports provided to them, especially reports from other clinical sites in multi-center trials. IRBs were concerned that the report volume impeded IRBs' ability to determine what actions, if any, should be taken to protect human subjects. The guidance addresses these concerns by clarifying the recommended roles of investigators, clinical study sponsors and IRBs in the analysis and reporting of adverse events, and is intended to ensure that only specific adverse events are reported to IRBs.

The final guidance, which includes few substantive changes from the FDA's April 2007 draft guidance, provides several notable clarifications or indications of areas where the FDA will exercise its enforcement discretion:

- The FDA clarifies that "unanticipated problems" reportable to the IRB generally include only those adverse events that are unexpected, serious, and have implications for the conduct of the trial, such as requiring a change in the protocol, monitoring requirements, or informed consent.
- The guidance directly addresses reporting of adverse events in multi-center trials. The FDA recognizes that the significance of any individual adverse event may not be apparent without evaluation of aggregate information from similar events across the study. The guidance therefore suggests that investigators engaged in multi-center studies are not required to submit to local IRBs each individual adverse event report received from the sponsor pertaining to subjects at other sites. Instead, in an important statement of a sponsor's obligations to investigators, the FDA states that an investigator may rely on a sponsor's assessment of whether an adverse event is in fact an "unanticipated problem" that should be reported to the IRB.
- Under the guidance, investigators may provide summary reports prepared by the sponsor to the IRB in lieu of individual reports and, when the sponsor and IRB have explicitly agreed that the sponsor will provide adverse event information directly to the IRB, the FDA will not require an investigator to provide a duplicate report to the IRB.
- The FDA also indicates that the clarification on investigator and sponsor reporting obligations applies both to investigational drug trials under 21 C.F.R. Part 312 and to investigational device trials under 21 C.F.R. Part 812.

The FDA's adverse event reporting guidance will have effects on the conduct of clinical trials and the relationships between sponsors, investigators, and IRBs. The guidance clarifies a sponsor's obligations pertaining to the reporting of adverse events discovered during the clinical trial process, and shifts some of the burden of analyzing and reporting adverse events from the clinical investigator to the study sponsor.

- IRBs should review their adverse event reporting policies to ensure that the reporting requirements do not prevent investigators from providing summary reports from sponsors instead of individual adverse event reports.

- Investigators should be trained on the applicable adverse event reporting policies and clarify with the institution and IRB what types and formats of adverse event reports must be submitted to the IRB and when the investigator can rely on the sponsor's actions to fulfill the investigators reporting obligations.
- Institutions conducting industry-sponsored trials and pharmaceutical or device manufacturer sponsors should ensure that adverse event reporting responsibilities are clearly set forth in clinical trial agreements, especially in the context of multi-center trials.
- Pharmaceutical sponsors should also understand the relevance of the guidance to the obligations under the Food and Drug Administration Amendments Act of 2007 (FDAAA), and should regard the analysis of adverse event information obtained from clinical trials in preparation for reporting to IRBs as an opportunity to develop risk management methods as part of the overall drug development program. The FDAAA and its component sections increase FDA authority to mandate safety-related conduct, and establish risk management as a keystone of regulatory authority throughout the drug development process. The potential risks identified by the reporting of "unanticipated problems" may be a trigger for regulatory action under FDAAA, including the possible imposition of formal Risk Evaluation and Mitigation Strategies (REMS) as a condition of approval, upgraded warning language in the approved labeling, special healthcare professional communications, or restrictions on distribution and use of the drug.

If you have any questions about adverse event reporting in clinical trials, related institutional or IRB policies, or the impact of the FDAAA provisions on the drug development process, please contact your usual Ropes & Gray advisor.