Adverse Event Reporting Requirements Clarified under New HHS Guidelines

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On January 15, 2007, the Department of Health and Human Services (HHS) Office of Human Research Protections (OHRP) released new clinical trial guidelines on reviewing and reporting unanticipated problems and adverse events that occur in clinical trials conducted or supported by federal departments or agencies.[i] The guidance comes in response to long-standing calls by Institutional Review Boards (IRBs) and the research community for harmonized federal guidelines on the reporting of clinical trial adverse events.[ii] To that end, OHRP developed the guidelines as an "initial step" with input from representatives of several federal agencies, including the Food and Drug Administration (FDA). The guidelines are intended to provide clarification of existing regulations and policies governing clinical trial adverse event reporting for IRBs, investigators and others involved in running clinical trials.

Current HHS regulations require that all "unanticipated problems involving risks to subjects or others" be reported to the OHRP.[iii] The guidance is intended to clarify what constitutes an "unanticipated problem" and ensure that such events are reviewed and reported in a timely, meaningful way so as to best protect human subjects. According to the guidance, an "unanticipated problem" under 45 C.F.R. Part 46 is an "incident, experience, or outcome" that: (1) is unexpected in terms of nature, severity, or frequency given the research procedures and the characteristics of the study population; (2) is related or possibly related to the participation in the research; and (3) suggests that the research places subjects or others at a great risk of harm, including psychological, economic, or social harm, than was previously known or recognized.[iv] The guidance stresses, however, that only a "small subset" of adverse events will constitute unanticipated problems.

OHRP considers an adverse event "unexpected" under the first criterion if it occurs "in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either: (1) the known or foreseeable risk of adverse events associated with the [research] procedures...; or (2) the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event." Under the second criterion, an adverse event is "at least partially caused" by the research procedures if it is "related" to participation in the

research; likewise, an adverse event is "possibly related" if there is a "reasonable possibility that the adverse event may have been caused by the procedures involved in the research." Lastly, the guidelines advise that if the adverse event is "serious" (*e.g.*, one that results in death, is life-threatening or results in inpatient hospitalization or a persistent or significant disability/incapacity), it will generally qualify under the third criterion (suggesting that the research places subjects at a greater risk of harm than was previously known or recognized). Furthermore, the guidelines provide several specific clinical examples of adverse events that constitute unanticipated problems.

If an unanticipated problem occurs, OHRP notes that it will "generally warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions" in order to create awareness of the newly identified risks and "protect the safety, welfare, and rights of subjects and others." Corrective action could include adjustment of the inclusion or exclusion criteria, suspension of the enrollment of new subjects, and implementation of additional monitoring procedures.

Other Considerations

The guidelines also expound on other considerations related to reviewing and reporting unanticipated problems and adverse events, including: which internal and external adverse events should be reported by investigators to IRBs; the content of the reports of unanticipated problems submitted to IRBs; the timing of reporting unanticipated problems; what an IRB should consider before, beginning, and during research with regards to adverse events; and how written IRB procedures should address unanticipated problems.

Conclusion

Companies should review the guidelines closely to ensure compliance with HHS reporting requirements, but should also note that for some research, the FDA and other agencies may still have distinct regulatory and policy requirements on reporting adverse events and unanticipated problems.

[i]*See* http://www.hhs.gov/ohrp/policy/AdvEvntGuid.htm.

[ii] OHRP, *Request for Public Comment on OHRP's Draft Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others* (Oct. 13, 2005), *available at* http://www.hhs.gov/ohrp/requests/com101105.html.

[iii] 45 C.F.R. § 46.103.

[iv] HHS, *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events*, 4 (Jan. 15, 2007).