Statement in Support of the Food and Drug Administration's
Guidance for Clinical Investigators, Sponsors, and IRBs
Adverse Event Reporting to IRBs – Improving Human Subject Protection

In January 2009, the Food and Drug Administration ("FDA" or "Agency") published a procedural guidance document entitled "Guidance for Clinical Investigators, Sponsors, and IRBs; Adverse Event Reporting to IRBs – Improving Human Subject Protection" ("Guidance"). The Guidance provides recommendations for sponsors and investigators conducting clinical research on how to identify adverse events ("AE") which also are "unanticipated problems" that must be reported to the institutional review board ("IRB"), and how that information is best conveyed to the IRB.

The Consortium of Independent Review Boards ("CIRB®") has reviewed this Guidance and believes that the measures and principles set forth in the document enhance the ability of IRBs to appropriately assess and respond to risk information. Further, adoption of these measures will reduce the receipt of event reports that do not provide sufficient information for such an assessment. Receipt of improved risk information will allow the IRB to better understand the impact of the event on human study participants, and whether changes are necessary to protect such subjects. Thus, CIRB wholeheartedly supports industry adoption of procedures consistent with the Guidance for the reason that such procedures hold the promise of providing improved safety for research participants.

During the course of a clinical trial, FDA regulations require investigators to report promptly to the IRB all unanticipated problems involving risks to human subjects or others. *See* 21 C.F.R. § 56.108(b)(1), § 312.53(c)(1)(vii), and § 312.66. As noted in the Guidance, "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." *See* Guidance, p. 3. CIRB agrees with the Agency's conclusion that an individual AE incident ***"ordinarily"*** does not meet these criteria, and that many types of AEs require an evaluation of their "relevance and significance to the study," prior to being determined to be unanticipated problems involving risk to human subjects. As such, CIRB echoes FDA's recommendation that sponsors and investigators carefully consider whether an AE is an unanticipated problem that must be reported to the IRB. *Id*. at 4.

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Further, CIRB agrees with FDA's determination that only the following AEs should be considered "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.
- 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.
- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem.
- 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.
- 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.
- 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 protection of human subjects.

See Guidance, pp. 4-5.

CIRB also concurs with FDA's conclusion that in 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." *Id*. at 5. In recognition of the sponsor's superior position in the review of risk information, the Guidance states that an investigator in a multi-center study can "rely on the sponsor's assessment and provide to the IRB a report of the unanticipated problem prepared by the sponsor." *Id*. at 5. In the alternative, FDA states that it will allow the sponsor to directly report unanticipated problems to the IRB as long as the sponsor, the investigator, and the IRB enter into a written agreement setting forth the reporting responsibilities, and the agreement further specifies that the investigator will receive a copy of such reports. CIRB supports the adoption of either approach for processing, analyzing, and transmitting risk information to the IRB.

In conclusion, in the interest of improving research participant safety, CIRB strongly encourages sponsors, investigators, and IRBs to adopt procedures consistent with this Guidance.