THE UNIVERSITY OF UTAH

INSTITUTIONAL REVIEW BOARD
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September 22, 2009

To Whom It May Concern

Re: University of Utah Institutional Review Board (IRB) Standard Operating Procedure (SOP) 901 – Unanticipated Problems Involving Risks to Participants or Others

University of Utah IRB SOP 901 complies with the reporting requirements set forth in Title 21 of the Code of Federal Regulations (21 CFR) 19 part 56 (Institutional Review Boards), part 312 (Investigational New Drug Application), part 812 (Investigational Device Exemptions), and Title 45 Code of Federal Regulations Part 46. FDA Guidance for Clinical Investigators[1], Sponsors[2], and IRBs Adverse Event Reporting Improving Human Subject Protection released in April 2007 notes:

> [The IRB community is concerned about the] 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.
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> 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.
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> 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

[1] 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

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

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"

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)). As such, It is the policy of the University of Utah IRB to require researchers to submit reports of events that may represent unanticipated problems involving risks to participants and others including unexpected and related adverse events. The IRB provides comprehensive guidance to investigators regarding this policy on the IRB website. FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting Improving Human Subject Protection released in April 2007 notes:

> 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…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).
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> 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…
- 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.

The IRB acknowledges that local investigators must rely on the sponsor of a multi-center study to provide information about adverse experiences that occur at other study sites. The sponsor has access to information from all study sites and may be in a better position to process and analyze the significance of adverse event information from those sites to determine whether an adverse event is an unanticipated problem.

However, the IRB has observed that sponsors often submit reports, or prompt local investigators to submit reports, that do not represent unanticipated problems. As a result, the IRB has determined that the local investigator must work closely with the sponsor and conduct a thorough evaluation to determine whether an event should be reported to the IRB. The IRB acknowledges the importance of sponsor expertise, local expertise, and the use of best medical as well as scientific judgment to make this determination. The local Investigator plays an important role in the reporting process and can help to ensure that events reported to the IRB are appropriate, significant and relevant to the study.

The University of Utah Human Research Protection Program (HRPP) has received full accreditation from the Association for Accreditation of Human Research Protection

Programs (AAHRPP), and SOP 901 has been vetted by AAHRPP, the University Office of General Counsel, the Veteran's Administration Health Care System of Salt Lake (also awarded full AAHRPP Accreditation), and the IRB Executive Committee. Please do not hesitate to contact me if I may be of assistance.

Sincerely,

John Stillman

John Stillman
Director
Institutional Review Board
University of Utah