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April 20, 2005

Via E-Mail [FDADockets@oc.fda.gov](mailto:FDADockets@oc.fda.gov)  
And hardcopy followup by U.S. Mail

Division of Dockets Management (HFA-305)  
Food and Drug Administration (FDA)  
5630 Fishers Lane, rm. 1061  
Rockville, MD 20852

Re: Comments on FDA's Hearing and Workshop - Reporting of Adverse Events to  
Institutional Review Boards (IRB) – 70 Fed. Reg. 6693, February 8, 2005 – **Docket  
No. 2005N-0038**

To the Food and Drug Administration:

Thank you for this opportunity to comment on the FDA's IRB adverse event reporting hearing and workshop (IRB workshop).<sup>1</sup> We are current or former volunteers, representatives of participants in human subject research, on authorized Community Advisory Board (CABs) which review government sponsored clinical trials testing vaccines to fight HIV/AIDS. Along with others, we submitted comments previously to FDA on proposals related to this workshop such as the Proposed Rule addressing safety reporting requirements for human drug and biological products (68 Fed. Reg. 12406, March 14, 2003 – Docket No. 00N-1484 (Safety Reporting Rule or SRR)). FDA's effort to increase efficiency in the ways IRBs participate in clinical trial monitoring and oversight, including responsible ways to manage the volume of adverse event reporting to IRBs and to improve the quality of reportable information, is a welcome initiative.

We understand, as FDA states, that investigators must report to IRBs all *unanticipated problems* involving risks to human subjects pursuant to 21 C.F.R. §312.66.<sup>2</sup> However, that reporting standard is not the same as (is not duplicative of) sponsors' obligations to report *serious and unexpected adverse events* promptly to FDA under 21 C.F.R. §312.32(c). The FDA's IRB workshop notice mentions also that site investigator conduit reporting of serious and unexpected adverse events to IRBs in a multicenter trial is discretionary not mandatory.<sup>3</sup> FDA's regulations are unclear how adverse event reporting is to be effectively channeled and organized by conduit or how relevant information from all sites in multicenter trials must be conveyed to each site IRB.

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<sup>1</sup> Unless stated otherwise, all cited page references will refer to the February 8, 2005 notice in the Federal Register.

<sup>2</sup> p. 6694.

<sup>3</sup> *ibid.*

Because of those uncertainties, previous comments requested that FDA make reporting of serious and unexpected adverse event information *to IRBs* a required component of reporting under 21 C.F.R. §312.32(c) when it revises its SRR.<sup>4</sup> That request bears repeating for the IRB workshop. Serious and unexpected adverse events required to be reported to FDA should be submitted also to IRBs. In the case of a multicenter trial, clear responsibility for the obligation (either investigator or sponsor) should be defined.<sup>5</sup> Considerations of volume and practicality may, on occasion, mitigate the need to make reporting of all serious expected adverse events to IRBs in the same fashion.

The SRR comments addressing ways to define “serious” or unexpected adverse events are also pertinent to these IRB workshop issues. Until FDA resolves the scope of reportable serious adverse event information under its SRR proposal, uncertainty will remain about the volume and quality of information most useful to IRBs. We request that FDA clarify the scope of reportable information by responding to the numerous comments it received on the SRR. That effort will help identify the volume and quality of information IRBs will find useful.

We are also concerned that high volume adverse event reports may result in a tendency to supply too much or perhaps the wrong kind of interpretive conclusion about the causes of adverse events. Those conclusions may interfere with the IRB’s valuable objective oversight review function. Investigators or sponsors may conclude that events are not or probably not caused by or related to study agents for various – and important – reasons. However, their conclusions should not be considered absolutely dispositive by the IRB. IRBs should retain freedom – and should be reminded - to reach different conclusions as to causation and offer independent assessments if they are justified. Any recommendations arising out of this workshop to proscribe interpretation of reportable information<sup>6</sup> should preserve the independence of IRB assessment.

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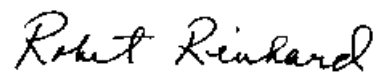
<sup>4</sup> SRR comments sent under joint signature with other groups were submitted to the docket and dated October 10, 2003.

<sup>5</sup> On March 28, 2005, FDA announced availability and comment opportunity for new guidance, “Using a Centralized IRB Review Process in Multicenter Clinical Trials,” (70 Fed. Reg. 15635). The guidance is not limited to adverse event reporting and addresses many topics affecting centralization. To the extent the guidance affects adverse event reporting, issues in these workshops should be noticed and incorporated. Separate comments may address centralization.

<sup>6</sup> p. 6694.

Thank you for consideration of these requests. The contact person for this letter is Robert Reinhard (Tel: 415/268-7469; email: [reinhard@mofocom](mailto:reinhard@mofocom)) for questions or response you may have.

Very Truly Yours,

A handwritten signature in black ink that reads "Robert Reinhard". The signature is written in a cursive, slightly slanted style.

Robert Reinhard, San Francisco Department of  
Public Health, HIV Vaccine Trials Network CAB  
and signing for,

Paul Williams, M.D., St. Louis University, HIV Vaccine Trials Network CAB

Gail Broder, MPH