

**FDA Public Hearing on
Reporting of Adverse Events to
Institutional Review Boards
(21 March 2005)**

*Presentation of Maureen Donahue Hardwick, Esquire
on behalf of the IRB-Sponsor Roundtable*

Introduction

- Pleased to speak today on behalf of the IRB-Sponsor Roundtable
 - The Roundtable commends FDA for organizing this hearing on this critical issue
 - Purpose of this presentation is to share Roundtable's thoughts on possible best practices and potential new processes to the current challenge of AE reporting in multi-site clinical studies
 - Roundtable views expressed are still a “work in progress”

Presentation Overview

- Provide background on the IRB-Sponsor Roundtable
- Provide feedback on FDA's questions (70 Fed. Reg. 6693; February 8, 2005)
 - IRB's responsibilities in multi-site trials versus single-site trials
 - Types of AEs that IRBs should receive
 - How to enhance IRB's ability to assess implications of AEs for study subjects
 - Consolidated reports of AEs

IRB-Sponsor Roundtable: Background (I)

- In 2003, two meetings on HIPAA and clinical research issues brought IRBs and sponsors together
 - Two communities engaged in productive dialogue
 - Consensus that increased communication on broader clinical research issues needed to enhance protection of human research subjects
 - Both the IRB and sponsor communities, and the research enterprise in general, will benefit from a neutral and constructive venue outside of individual trials to address overarching and recurring issues
- Formed in 2004, the Roundtable is comprised of representatives from IRBs and Sponsors
 - Independent of existing organizations (*e.g.*, P/RMA, PRIM&R, ARENA, DIA)
 - Goal is equal representation from both communities

IRB-Sponsor Roundtable: Background (II)

- The Roundtable is the first organization where sponsors and IRBs have come together as equal partners to address issues of mutual concern in a sustained and task-oriented manner
- This new paradigm for communication may improve the functioning of IRBs and sponsors in their respective roles in large and increasingly complex research projects
 - The current challenges associated with AE reporting in multi-site trials is a Roundtable priority

Roundtable's Mission

- Facilitate constructive communications between sponsors and IRBs on significant clinical research issues and, where possible,
 - propose practical strategies for improving clinical trial processes and human subject protections
 - engage other affected stakeholders to facilitate broader dialogue and consensus building
- Overarching objective: Enhance protection of human research subjects

Roundtable Participants

■ IRBs:

Marianne Elliott

Navy Medical Research

Karen Hansen

Fred Hutchinson Cancer Research Ctr

Moira Keane

University of Minnesota

Pearl O'Rourke

Partners Healthcare System

Ada Sue Selwitz

University of Kentucky

Felix Gyi

Chesapeake Research Review, Inc

John Isidor

Schulman Associates IRB

Daniel Nelson (Co-Chair)

University of North Carolina

Ernest Prentice

University of Nebraska

■ Sponsors:

■ Pfizer (Justin McCarthy, Co-Chair)

■ Sanofi-Aventis

■ Novartis

■ Schering-Plough

Current Context

- Clinical investigation of FDA-regulated products are frequently conducted at numerous sites across the US and around the world
 - Often each study site is overseen by a different IRB; IRB receives individual reports of expedited AEs (including possible unanticipated problems involving risks to human subjects and others) reported in subjects enrolled in: its institution and other institutions in the same trial
 - Sheer number and disaggregated nature of reports make it difficult, particularly for IRBs, to effectively evaluate significance and the implications for study subjects

Current Context, Cont.

- Existing regulatory framework developed before multi-site trials were commonplace
- Regulatory definitions and processes for AE reporting differ among FDA and other agencies
- **Process would benefit from clear regulatory guidance relevant to multi-site trials**

Some Definitions

- “Adverse Event” or “Adverse Experience” (AE)
 - Multiple definitions exist (e.g., FDA’s IND regulation, ICH guidelines)
 - **External AE:** In a multi-site trial an AE that occurs at an institution other than the one for which the IRB is directly responsible
 - **Internal AE:** In a multi-site trial, an AE that occurs at the local IRB’s institution, not one of the other sites involved in the trial
- “Unanticipated problems involving risks to human subjects or others” (21 CFR 56.108 and 45 CFR 46.103): broader than AEs, but significant overlap exists

Definitions, Cont.

- Data Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC): Formal committees charged with reviewing the accumulating data as the trial progresses to:
 - Monitor safety, effectiveness, and trial conduct issues
 - Provide a set of recommendations to study Sponsor

Goals of a New AE Model

- Enhance protection of human subjects by ensuring that medically relevant data on AEs is communicated to IRBs in a meaningful way
 - Clearly highlight medically relevant events that are more likely to change risk/benefit relationship from other AEs
- Promote responsible and effective AE reporting through a multi-party process (IRBs, Principal Investigators and Sponsors) which includes appropriate checks and balances
 - Reinforce active participation by all parties in identifying potential unanticipated problems

IRB's Review of AEs in Multi-site Trials

- IRBs are not intended to function as safety oversight committees for multi-site trials
- IRBs do not have access to the relevant information necessary to evaluate large volumes of disaggregated “external” AE reports in order to put them in proper context
- At present, the signal to noise ratio is unfavorably dominated by noise for review by IRBs
- **The process for sending routine expedited “external” AE reports to IRBs should be eliminated**

Possible Elements of Solution

- In context of identifying unanticipated problems involving risks to human subjects, **Investigators** should identify “relevant” external AE reports that require notification to IRB
 - **Proposed criteria** for “relevant” reports:
 - Reports leading to study protocol modification
 - Reports leading to revisions to informed consent form
 - Reports reflective of (other) major concerns impacting the study
 - Note:
 - PI’s obligation to submit all appropriate internal AEs is unchanged
 - Sponsors should continue to submit expedited AE reports to FDA pursuant to existing regulatory requirements

Possible Elements of a Solution (II)

- **Sponsors** should clearly identify to PI those external AE reports that meet criteria
 - Supplements Sponsors' existing safety reporting obligations to FDA and PI
 - Best practice (as such reports are usually singled out)
- Importantly:
 - PIs should provide AE reports to IRBs that they believe meet the criteria for notification of IRBs, even if sponsor does not identify them as such
 - If PI believes AE reports not meeting the criteria should be sent to the IRB, they should do so providing justification for the transmission
 - If the Sponsor concludes that an external report warrants immediate referral to IRB, it should highlight to PIs

Other Best Practices & Checks and Balances

- Sponsors and Principal investigators should document their analysis of all external AEs
 - This analysis and associated documentation would be subject to audit by the IRB (or designated compliance arm) for Investigator site and by FDA for both Sponsors and Site Investigators
- Sponsor should develop and justify a plan and schedule for communicating aggregate AE reports as part of the study protocol

Plan for Communicating AEs

- In the study protocol submitted to IRBs, the Sponsor should specify a “communication plan” for providing periodic aggregate summaries of external AEs
- Elements of the plan *could* include:
 - Proposed frequency for submission of aggregate safety information (*i.e.*, quarterly, semi-annual, or annual)
 - Proposed format for the submission of periodic qualitative assessment reports covering all safety information relevant to the trial, including all expedited AEs and other relevant safety information
 - Description of the functioning of a DSMB, if used for the study, and the method & frequency of communication of DSMB reviews to Investigators/IRBs
- Should be developed and implemented in a flexible manner to meet the specific needs of an individual clinical trial/Investigational product

Suggested Next Steps

- The Roundtable will:
 - Continue to discuss and further refine thinking on AE reporting and role of IRBs in multi-site trials
 - Reflect on submissions during this Hearing
 - Consider existing proposal by CIOMS VI
 - Conduct outreach to interested stakeholders (e.g., P/RMA, ARENA, PRIM&R, investigators) to obtain feedback
 - Particularly important to obtain input from investigators
 - As appropriate, continue dialogue with interested government agencies
 - Priority: submission of written comments by 21 April 2005
- The Roundtable encourages FDA/OHRP to clearly articulate – in official guidance – best practices for reporting of external AEs in multi-site clinical trials

Conclusions

- If a more workable AE reporting model for multi-site trials is put in place:
 - IRBs will be able to more effectively evaluate risk/benefit issues
 - Both Investigators and Sponsors will be better equipped to fulfill their regulatory and ethical responsibilities
 - Subject protection will be enhanced