



June 7, 2007

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

RE: Guidance for Clinical Investigators, Sponsors, and IRBs on Adverse Event Reporting – Docket No. 2007D-0106

Submitted electronically to: <http://frwebgate.access.gpo.gov/cgi-bin/leaving.cgi?from=leavingFR.html&log=linklog&to=http://www.fda.gov/dockets/ecomments> on June 7, 2007

Dear Sir/Madam,

On behalf of Public Responsibility in Medicine and Research (PRIM&R), we appreciate the opportunity to comment on the above referenced Guidance.

PRIM&R is an educational organization dedicated to creating, implementing, and advancing the highest ethical standards in the conduct of research. Its members represent a diversity of institutions and individuals throughout the world whose research efforts vary significantly. The membership includes a range of professionals from research administrators, government officials, and academic deans, to members and chairs of Institutional Review Boards (IRBs), Institutional Animal Care and Use Committees (IACUCs), and Institutional Biosafety Committees (IBCs).

PRIM&R congratulates FDA on the *Guidance for Clinical Investigators, Sponsors, and IRBs on Adverse Event Reporting*. We believe that the document represents a step forward in establishing a system for reporting adverse events that enhances protections for human subjects. PRIM&R welcomes the guidance on how to distinguish “unanticipated problems” from “adverse events,” and the recommendation that all reports to the IRB of unanticipated problems explain the relevance and significance of the problem to the study. Moreover, the recommendation for sponsors to process and analyze the implications and significance of adverse events that occur in multicenter studies will generate crucial information for IRBs.

We believe, however, that the policy could have provided additional guidance as outlined in PRIM&R’s comments submitted in response to the FDA’s solicitation of comments on the “Submission and IRB Review Process Related to Adverse Events” issued February

8, 2005. PRIM&R believes that those comments are still relevant and we incorporate them in this submission. (See attached comments submitted by PRIM&R's membership group, Applied Research Ethics National Association (ARENA)¹ dated April 21, 2005, hereafter referred to as "ARENA Comments"). Specifically, PRIM&R requests further consideration of the following issues:

1. **Data and Safety Monitoring Plans:** The Guidance fails to address the role of the Data and Safety Monitoring Board and Data and Safety Monitoring Plans (DSMPs) in the process of reporting adverse events. The ARENA Comments request guidance on the elements of an optimal DSMP that would encourage consistent and enhanced reporting of adverse events.
2. **Harmonization of FDA and HHS Regulations Related to "Unanticipated Problems":** The new Guidance fails to address the inconsistency among the various federal regulations that relate to adverse events and unanticipated problems. As noted in the ARENA Comments, there are at least three sets of regulations that are relevant: 21 CFR 56.108, 21 CFR 312 (multiple sections) and 45 CFR 46.103. In addition, the new FDA Guidance fails to address the new OHRP *Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events* issued in January of this year. Lack of harmonization among these regulations will allow confusion and inconsistent reporting of adverse events to endure ultimately undermining protections for human subjects.

For example, the FDA Guidance recommends that "there be careful consideration of whether an adverse event is an unanticipated problem that must be reported to IRBs." It also describes four categories of events that might be considered "unanticipated problems." The OHRP Guidance provides more detailed guidance on what constitutes an "adverse event," and "unanticipated problem," and how to determine whether certain events meet the detailed criteria for each. Even if the two guidance documents are not contradictory, the failure to illuminate the differences between them will result in confusion and inconsistent reporting.

Thank you for your consideration of these comments.

Respectfully submitted,



Pearl O'Rourke, MD
Chair, PRIM&R Board of Directors

¹ The ARENA Membership, since the date of these comments, has been absorbed by PRIM&R and the "ARENA" name is no longer in use. PRIM&R continues to serve a growing and active membership.

ATTACHMENT



April 21, 2005

US Food and Drug Administration
Division of Dockets Management (HFA-305)
5630 Fishers Lane, Room 10061
Rockville, MD 20852

RE: Docket No. 2005N-0038
Reporting of Adverse Events to Institutional Review Boards

To whom it may concern:

On behalf of the Applied Research Ethics National Association (ARENA), we appreciate the opportunity to comment on the submission and IRB review process related to adverse events information discussed in the Federal Register, February 8, 2005, Volume 70, Number 25.

ARENA is the membership division of Public Responsibility in Medicine and Research (PRIM&R), an educational organization dedicated to creating, implementing, and advancing the highest ethical standards in the conduct of research.

ARENA's mission is to enhance human and animal research subject protections and the responsible conduct of research through the educational and professional development of its members. Members represent a diversity of institutions throughout the world whose research efforts vary substantially. ARENA's membership includes a range of professionals from research administrators, government officials, and academic deans, to members and chairs of Institutional Review Boards (IRBs), Institutional Animal Care and Use Committees (IACUCs), and Institutional Biosafety Committees (IBCs).

We have the following comments to offer:

- A. IRB Review of Data and Safety Monitoring Plans
- B. ARENA's responses to the FDA's request for comments on *Reporting of Adverse Events to Institutional Review Boards*. These comments supplement the testimony provided by David Borasky on behalf of ARENA at the FDA public hearing on March 21, 2005.

A. IRB Review and Approval of Data and Safety Monitoring Plans

Federal regulations state, "where appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects," at 21CFR 56.111(a)(6) (FDA regulations) and at 45 CFR 46.111(a)(6) (HHS regulations). NIH policy (NIH Policy for Data and Safety Monitoring, June 10, 1998) recommends that all clinical trials include a *data and safety monitoring plan*, further indicating that the monitoring plan should be tailored to the nature, size and complexity of the clinical trial. Therefore, the IRB's role is to ensure that there is an appropriate *data and safety monitoring plan* in place at the time of initial approval and to ensure that the plan continues to be in place during the life of the protocol. These plans, which should be reviewed and approved by the IRB of record, should articulate the adverse event reporting requirements and methods for communicating these events in a coherent, understandable manner to the investigators and staff responsible for conduct of the trials.

For example, at the time of initial approval the IRB confirms that based on the nature, size and complexity of the trial that the data and safety monitoring plan appropriately describes:

- who will conduct the scientific evaluations (e.g. DSMB or investigator and biostatistician),
- the frequency of the analysis,
- when and how the stopping rules will be invoked,
- how and when participating investigators and the IRBs will be apprised of the results of the periodic assessments, particularly as they relate to timely communication of unexpected, serious adverse events that are reasonably related to the study procedures, as well as the nature and scope of the cumulative report of adverse events to be provided at the time of continuing review.

Given the importance of a sound data and safety monitoring plan, ARENA's responses to the FDA's request for comments on *Reporting of Adverse Events to Institutional Review Boards* will frequently reference the data and safety monitoring plan (DSMP) as the vehicle used to articulate reporting requirements. We strongly recommend that the FDA and HHS develop a harmonized and efficient reporting model for serious, unexpected and reasonably related adverse events that can be adapted for use, as appropriate in each multi-site trial. The model reporting mechanism would assure submission of meaningful and timely summary information to the IRB of record for a study. The model adverse event reporting mechanism, at a minimum, should include and address reporting requirements, as appropriate, for each of the following parties responsible for human subject protection:

- Sponsors (i.e., pharmaceutical companies, biotechnology companies, investigators holding investigator-sponsored INDs, and agencies or institutes within the Department of Health and Human Services)
- IRBs (institutional or central IRBs), and
- Performance site investigators.

The adverse event reporting system included in each protocol's data and safety monitoring plan would provide a common understanding of the pathways and time frames for adverse event reporting. This approach would enhance research subject protection by clarifying reporting expectations and responsibilities for all parties involved in the conduct and the oversight of the research protocol. It would also have the potential for reducing redundancy of duplicative reporting of single case, ad hoc, adverse events from sponsors to performance site investigators and their IRB of record participating in multi-site trials.

Attachment A , Points to Consider, is a resource that can be adapted for use by protocol development teams to help them address protocol reporting requirements in the protocol's DSMP. The same document could also be adapted for use by an IRB evaluating a new study. If requested, ARENA could also provide you other samples of DSMP assessment documents developed by IRBs and/or organizations.

B. ARENA's responses to the FDA's request for comments on *Reporting of Adverse Events to Institutional Review Boards*. These comments supplement the testimony provided by David Borasky on behalf of ARENA at the FDA public hearing on March 21, 2005.

1. The Role of IRBs in the Review of Adverse Events Information from Ongoing Clinical Trials

a) *What role should IRBs play in the review of adverse events information from an ongoing trial?*

Response: The IRB should confirm that there is an appropriate Data and Safety Monitoring Plan (DSMP) for each study and that the DSMP thoroughly describes the adverse event reporting process to be followed (See Item A above).

b) How does this differ from the current role of IRBs?

Response: IRBs review the data and safety monitoring plan for each protocol as required by NIH policy and FDA/HHS regulations. However, a harmonized and efficient model for **reporting** serious, unexpected and reasonably related adverse events and/or unanticipated problems does not exist. Absent a harmonized approach, IRBs frequently receive disaggregated, single-case adverse event reports that:

- may or may not originate from the local performance site investigators, and
- may not provide the information necessary to assess whether the risk/benefit relationship is still appropriate and if the trial should continue as most recently approved.

c) Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?

Response: Ideally, an IRB determines whether a DSMP which includes adverse event reporting requirements, is appropriate for either a single-site or multi-site trial. When evaluating the DSMP, the IRB may encounter the involvement of a Data Safety Monitoring Board (DSMB) for single-site or multi-site trials or a Coordinating Center responsible for managing adverse events reporting in a multi-site trial. Because the make up and rules of operations for Data and Safety Monitoring Boards and Coordinating Centers are often study-specific, IRBs often need to request more information about the composition of the DSMB, frequency of meeting, and methods for communicating serious, unexpected and reasonably related adverse events as well as aggregate trialwide summary findings to the IRB.

Additional considerations for an IRB might include the following, as appropriate:

- If an IRB is affiliated with the coordinating center of a multi-site trial, they should also determine the extent to which they have any obligations to the IRBs of other participating institutions.
- If an IRB is a non-coordinating site, they can determine the extent to which they would require trial wide reports for their review from the coordinating center IRB.

2. The types of adverse events about which IRBs should receive information.

a) What types of adverse events should an IRB receive information about, and what types of information need not be provided to IRBs? For example, should IRBs generally receive information only about adverse events that are both serious and unexpected?

Response: As a brief introduction to question 2, it should be noted that the human subjects regulations at 21 CFR 56.108(b)(1) (FDA) and at 45 CFR 46.103 (b)(5)(i) (HHS) are nearly identical and indicate "...prompt reporting to the IRB, the appropriate institutional offices and the FDA/Department or Agency Head of any unanticipated problems involving risks to human subjects or others," with no threshold for severity or attribution, whereas the IND regulations at 21 CFR 312.32(c)(1)(A) indicate that "the sponsor shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected." The latter IND regulation indicates a threshold as well as

attribution. All applicable federal regulations should be harmonized so that reporting requirements are consistent and are based on threshold, attribution and expectedness. The lack of harmonization may be, in part, a root of the problem. Any information that would indicate a change in the risk/benefit ratio and any information that would mandate a change in the consent document should be reported. More express examples of criteria for reporting follow.

Following initial approval and throughout the conduct of the research, the IRB should be notified (via the principal investigator who has a prima facie duty to the research subject) of only those individual external (multi-site trials) and local (for both single-site and multi-site trials) adverse events that are:

- serious and unexpected (including frequency and magnitude), and
- deemed to be reasonably related to the research procedures

The reporting of unexpected, serious and reasonably related adverse event definition, should result in a recommendation from the sponsor or the local principal investigator to revise the protocol, modify the consent form, inform or advise currently enrolled subjects of the new information, suspend accrual, etc.

At the time of IRB continuing review (e.g. review process that occurs once every 365 days or more frequently, if specified by the IRB), all cumulative data that has been collected and analyzed since trial inception, should be presented to the IRB in aggregate form with a summary statement indicating whether cumulative data indicated any adverse change in the assessment of subject safety, whether the consent document should be changed or whether the research should continue as planned.

b) Are there circumstances under which IRBs should receive information about adverse events that are not both serious and unexpected (e.g., if the information would provide a basis for changing the protocol, informed consent, or investigator's brochure)?

Response: In general, the principal investigator who has the requisite expertise should make this determination. The principal investigator must report his/her findings to the IRB and make specific recommendations for modifying the consent document or informing subjects currently on study of any new information. It should be noted that in sponsored multi-site trials, modification of the protocol would be done by the sponsor and not the principal investigator.

c) In a multicenter study, should the criteria for reporting adverse events to an IRB differ, depending on whether the adverse events occur at the IRB's site or at another site?

Response: Yes. A summary of a multi-site clinical trial's adverse events and/or unanticipated problems should be prepared by a review group with the scientific expertise (e.g., a Data and Safety Monitoring Board) and the charge to evaluate all information regarding reported adverse events. Issues such as stopping a study, changing a procedure, eliminating an agent, or providing additional information to subjects should be the responsibility of this review group in collaboration with the Sponsor. The FDA, principal investigators and local IRBs should receive the aggregate report with guidance on how to apply that information to their local populations. The role of IRBs should be to evaluate the implications of aggregate information provided to them, apply that information to the local populations, and take appropriate action to ensure subject safety. Multi-center studies typically have a central coordinating site to which all adverse events are reported. Again, the data should be reviewed and disseminated by the central coordinating site to principal investigators and thereafter to the IRBs in aggregate form, with summary recommendations and as indicated above as part of the approved protocol's data safety monitoring plan. Most IRBs of record do specify the timeframe for prompt notification by its investigators of all serious, unexpected and reasonably related adverse events that are experienced by the research subjects directly under its purview for either a single-site or multi-site trial.

3. Approaches to providing adverse events information to IRBs.

a) There seems to be a general consensus in the IRB community that adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not informative to permit IRBs to assess the implications of reported events for study subjects. What can be done to provide IRBs adverse event information that will enable them to better assess the implications of reported events for study subjects? For example, if prior to submission to an IRB, adverse event reports were consolidated or aggregated and the information analyzed and/or summarized, would that improve an IRB's ability to make useful determinations based on the adverse event information it receives? If so, what kinds of information should be included in consolidated reports? And when should consolidated reports be provided to IRBs (e.g., at specified intervals, only when there is a change to the protocol, informed consent, or investigator's brochure due to adverse events experience)? Who should provide such reports?

Response: Yes, reports in which data has been consolidated, analyzed, and summarized would significantly improve the IRB's ability to appropriately assess the information in light of its' knowledge of the trial.

In summary, and as noted in responses 1 and 2 above, the IRB should receive individual reports only when the adverse event or problem meets the three criteria of unexpected, serious and reasonably related (to study procedures). The IRB should determine that the data and safety monitoring plan that is tailored to the nature, size and complexity of the clinical trial is approvable at the time of initial review. At continuing review, the IRB should receive an aggregate summary report from the responsible person(s)— as outlined in the data and safety monitoring plan that indicates the adverse event experience (expected and unexpected adverse events) thus far. Both the individual reports and the aggregate reports should provide the IRB with guidance and recommendations regarding the statistical relevance of the events and whether the study should continue based on the data and safety evaluation. If a single adverse event or interim analysis specified in the data safety monitoring plan prompted the sponsor or investigator-sponsor to temporarily close the research to new subject accrual or require modification of the protocol, informed consent document, or investigator brochure, the IRB should be notified by the local principal investigator as soon as possible after he/she has been made aware of the situation.

b) Should the approach to providing IRBs adverse event reports be the same for drugs and devices?

Response: Yes, the approach to adverse event reports for drugs and devices should be consistent across all regulations, i.e., IND regulations, (21 CFR 312), IDE regulations (21 CFR 812), human subjects regulations (21 CFR 50, 56, and 45 CFR 46). For the purpose of harmonization, all adverse event reports should be subject to the same underlying regulatory requirements and stringencies, for the sake of efficiency and ultimately to assure minimization of risk and the protection of the health and welfare of research subjects.

SUMMARY STATEMENT:

We would like to reiterate the three major initiatives we endorse as consideration is given to developing an improved, effective and efficient adverse event reporting structure to ensure that IRBs are provided with meaningful information needed to protect the rights and welfare of human subjects. The recommended adverse event reporting initiative priorities are as follows:

1) A federally mandated and financed framework for multi-site trials that creates and implements a model for data and safety monitoring plans that includes a description of adverse event reporting requirements, and time frames for sponsors, investigators and IRBs. This could be accomplished, at least in part, by making the costs of such a plan a direct cost. These plans hold

great value in protecting subject safety and assuring that duplication of effort is avoided while assuring a positive safety-oriented approach to subject safety. (See Attachment A –Suggested **Points to Consider** document for developing a DSMP)

2) Harmonization of adverse event reporting guidelines, regulations and policy across federal agencies (See Attachment B - letter from Dr. Pearl O'Rourke dated April 21, 2005).

3) Development of federal guidelines and models for summary reporting of aggregate multi-site trial data to IRBs. Developing sample formats or models that could streamline and facilitate reporting of meaningful, summary trial-wide data findings prepared by sponsors or sponsor investigators for dissemination to IRBs.

Thank you for the opportunity to respond to these questions and provide testimony at the public hearing. ARENA would be pleased to have the opportunity to assist with development of an improved, effective and efficient adverse event reporting model. If you have any questions or require further information, please let us know.

Sincerely,
Pearl O'Rourke, PRIM&R Board Chair
Nancy Olson, ARENA Council Chair
Karen Hansen, Co-Chair, Public Policy Committee

Cc: Public Policy Working Group: Gwenn Oki, Pat Scannell, Norma Epley, David Borasky, Susie Hoffman, Mark Waxman, Paul Martin and Amy Davis.

***ATTACHMENT A - POINTS TO CONSIDER
SPONSOR DEVELOPMENT OF A PROTOCOL SPECIFIC DATA AND SAFETY MONITORING
PLAN₁ INCLUDING ADVERSE EVENT REPORTING₂ OR IRB REVIEW OF A DATA AND SAFETY
MONITORING PLAN INCLUDING ADVERSE EVENT REPORTING (if not provided in research
protocol)***

- *What regulations apply to this protocol?*
- *What are the funding sources?*
- *What are the risks?*
- *How are risks minimized?*
- *Who is monitoring for the risks?*
- *What are the mechanisms for reporting serious and non-serious adverse events?*
- *When and what types of adverse event reports are to be provided to the investigator, sponsor, and IRB, and in what sequence?*
- *How are aggregate adverse event data evaluated and at what frequency?*
- *Is there a DSMB?₃*

If yes, who serves on the Board, what is their charge, frequency of interim analysis and to whom do they provide reports? Does the DSMB have access to blinded data?

If no, who is responsible for the monitoring the trial? Specify and state their charge, frequency of interim analysis and to whom they provide monitoring reports.

- *Are the stopping rules and/or study endpoints appropriate and how are these invoked?*

OTHER CONSIDERATIONS AND RESOURCES:

1) Funding institutes, such as National Cancer Institute and the National Heart Lung and Blood Institute, may have more specific rules or requirements for DSMBs and monitoring plans.

2) *A Worksheet to Aid in Developing a DSMP* is included in the *Journal of Investigative*

***Medicine*, Volume 52, number 7, November and meant to accompany the Data and Safety Monitoring Plan series authored by Zucker, DR, Hibberd, P.L., Weiner, DL, Wittes, J, Terrin, ML, Martinez, RA**

¹ Zucker, Deborah R. Considerations in Developing Data and Safety Monitoring Plans: A Framework; *Journal of Investigative Medicine*, Volume 52, number 7, November 2004 pp. 443-445.

² Hibberd, Patricia L., Weiner Debra L. Monitoring Participant Safety in Phase I and II Interventional Trials; Options and Controversies; *Journal of Investigative Medicine*, Volume 52, number 7, November 2004 pp 446-451

³ Wittes, Janet, Forming Your Phase III Trial's Data and Safety Monitoring Board: A Perspective on Safety, *Journal of Investigative Medicine*, Volume 52, number 7, November 2004 pp 453-458.

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ATTACHMENT B - LETTER FROM DR. PEARL O'ROURKE

April 21, 2005

On behalf of PRIMR and ARENA we thank you for the opportunity to share thoughts, concerns and suggestions regarding the handling of adverse events in human research.

The goals of adverse event reporting are obvious:

- Individual research participants reasonably expect that research is monitored for safety and that they will be informed of all relevant details and risks at the time of enrollment as well as during the course of the research. If the risk-benefit analysis of their participation in the research changes, they should be informed and allowed to consider their continued participation in light of this new information.
- Investigators must clearly understand and fulfill their responsibility for evaluating as well as reporting adverse events. Investigators must know what to report, to whom, and in what time frame. Investigators must realize their 'role-specific-accountability' for all types of research; for example, investigator-initiated studies versus industry sponsored studies; single site versus multisite studies; adverse events that occur at a local site versus those that occur at distant sites.
- IRBs must feel comfortable that they are in timely receipt of information that may alter risk assessment or require re-contacting participants to ascertain their willingness to continue in the research. The information must be reliable, relevant, useful and presented in a comprehensive and comprehensible format.

But – meeting these goals is difficult. Current regulations are riddled with inconsistent language and inconsistent requirements that foster confusion and can lead to under as well as over-reporting. The system needs improvement – hence this request for comments. PRIM&R and ARENA have presented responses to the specific questions posted. I would like to add a few brief comments that embellish these responses.

First the need for harmonization:

Today the focus is FDA regulated research – but the topic of adverse event reporting does not respect that boundary. Study participants expect the same level of protection regardless of regulatory assignment to the FDA or the Common Rule. IRBs should not have to tier the level of protection as a function of specific regulatory construct. Please keep in mind that IRBs can best protect subjects if allowed to implement uniform definitions and rules for all research. Please harmonize – not only between the different centers at FDA – but between the institutes and centers at the NIH and other relevant federal agencies. Please provide: a standard definition of adverse event and levels of severity; a standard timeframe in which adverse events must be

reported; standard delegation of who must submit a report and to whom. Instructions that address all of these elements should be identical and easily accessible on all relevant regulatory websites.

Second - make certain the solution fits today's heterogeneous research paradigm:

While the challenges of multi-center research with numerous sites, numerous investigators and numerous IRBs scream for attention, remember, single-site investigator-initiated protocols still exist. Not all research involves an FDA-regulated product. Adverse events will occur in all research models – any solution must respect and be applicable to the entire spectrum.

Finally – make proposed solutions achievable – please consider the logistics and the necessary resources:

One suggestion for the handling of adverse events would be the routine use of a formal independent committee that receives all adverse events; assesses them; and reports summary data back to the investigator/s and other pertinent entities. This could be achieved with today's 'status quo' Data Monitoring Committees or with other similar constructs. While this is an attractive 'solution' – consider the fact that even now, investigators have difficulty identifying people willing to serve on DSMBs or even to serve in lesser oversight roles. If more independent monitoring is required - how will these people be found? Be paid? Be vetted as free of conflict of interest?

On behalf of PRIMR and ARENA – thank you for the opportunity to comment on this issue. We welcome the opportunity to work with you in the development of new guidance, policies or regulations that address the critical steps in handling adverse events.

Respectfully Submitted,
Pearl O'Rourke, Chair, Board of Directors
Public Responsibility in Medicine and Research