

Statement Regarding Adverse Event Reporting

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My name is Gary Chadwick. I am currently the Associate Provost and Director, Office for Human Subject Protection at the University of Rochester. My remarks, however, are my own and do not necessarily represent those of the University of Rochester. I have been at the University for over eight years and have been actively involved in managing, directing and overseeing its institutional review board (IRB) system for all of that time. Before joining the University, I was the Associate Director for Human Subject Protections in the FDA's Office of the Commissioner (Office for Health Affairs). Prior to that, I worked with Paul Goebel and Frances Kelsey in the Division of Scientific Review in the Center for Drug Evaluation and Research (CDER). Before then, I was in the Office for Protection from Research Risk, which became the HHS Office for Human Research Protection. Over 20 years of my professional life has been dedicated to improving health care and protecting human research subjects nationally and internationally. This is an area about which I care deeply.

I would like to add my voice to the chorus of people who maintain that having IRBs review all adverse event reports is completely unworkable. IRBs are not designed to perform this function and dumping this Sisyphean task on them has undermined the IRB system to the detriment of human subjects and to science as well.

The announcement for this public hearing states that, "FDA would like to understand better how the IRB's responsibility with respect to adverse events fit[s]." My position is that IRBs are not responsible for adverse event review and should not be expected to conduct this review.

Review of "adverse events" is a scientific duty. The determination that a study should be continued or modified or even stopped is the responsibility of investigators and sponsors – including federal agency sponsors. The role of the IRB in this process is to determine that the study and its related activities are justified and ethically appropriate. It is not the IRB's role to accomplish the adverse event review.

Granted, the FDA regulations for IRB operations (56.108(b)(1)) call for IRBs to receive reports of "unanticipated problems involving risk to human subjects." This term, however, does not equate to reviewing adverse event report forms. Most reported adverse events are anticipated or could reasonably be predicted and the risk they present is often unclear.

In the drug regulations (312.32(c)(1)(i)(A)), the FDA requires the sponsor to notify the FDA and participating investigators of adverse events associated with the use of a test article if it is "both serious and unexpected." Note that IRBs are not required to receive these reports. Unfortunately (from my point of view), the device regulations (812.150(a)(2)) state that "unanticipated adverse

device effects” must be reported by investigators to sponsors and to the reviewing IRB. This inconsistency has contributed to the current state of confusion about adverse event reporting. At least the term “unanticipated” was used, but to ensure the IRB system can work effectively, we need to get the phrase “adverse events” out of the IRB lexicon.

It is important to make three distinctions. First, that reporting “unanticipated problems” is not the same as sending adverse event report forms. Second, that the regulatory term “adverse event reports” should encompass more than just the adverse event reporting form. Third, that there is a difference between unanticipated problems and adverse events. There are vastly many more “adverse events” in research than there are “unanticipated problems.” IRBs need to focus on truly unanticipated problems and not on adverse event reports.

As the announcement for this hearing and the FDA regulations (56.109(f)) state, IRBs are responsible for conducting continuing review of research – “at intervals” – appropriate to risks. This periodic review is a “snapshot” of a study at points along its progress, i.e., whenever a change is requested or the study approval is extended – usually once per year. So, by regulation, IRBs must conduct a continuing review, but they were never intended to perform continuous monitoring.

Guidance documents and FDA regulations, particularly regarding devices, are partially responsible for the unworkable adverse event review situation that exists today. The requirement for reporting unanticipated problems has never been clear in either FDA or HHS regulations and IRBs, sponsors and investigators have struggled with its meaning for years. I believe that the term “reports of unanticipated problems” was intended to mean “summary reports,” with analysis and conclusions about the unanticipated problem and corrections to resolve the issue, not just simple reports of an occurrence, which may or may not have been predictable.

Misapplication, misinterpretation and/or misunderstanding of the FDA regulations have caused adverse event report forms to jam the void created by the lack of understanding about the reporting requirement for unanticipated problems. Despite having no regulatory basis, current (July 11, 2002) HHS guidance on continuing review (<http://www.hhs.gov/ohrp/policy/index.html#continuing>) states, “continuing review of research by the IRB should include consideration of adverse events” and even when a data safety monitoring board is in place, it says that “the IRB must still receive and review reports of local, on-site adverse events.” Fear is driving the system to be over-inclusive. So, instead of considered and useful summary reports from our investigators, IRBs receive stacks of duplicative raw data in hundreds of varying formats from dozens of sources. To make matters worse, investigators are inclined to merely pass these raw report forms on to the IRB without any thought as to their meaning or providing any expert opinion to the IRB.

Reviewing reams of adverse event report forms is not a task for which IRBs are equipped. This futile activity has added to the workload of IRBs, drained their limited resources and blurred the essential role that they play in human subject protection. Removing the responsibility for “adverse event” reviews would go a long way toward allowing IRBs to maintain focus on their central mission of ethical review and improve human subject protection. It is within the FDA’s power to rectify the current situation by clearly stating that submission of all adverse event report

forms to IRBs is neither required nor desired. This remedy could be quickly accomplished through guidance issued by FDA, preferably jointly with HHS. Long-term, the wording in the drug and device regulations needs to be amended to agree, and the human subject protection regulations in part 56 may need to be clarified.

FDA has asked that we address questions posed in three areas. The questions (Q) and my responses (R) follow.

Area 1. The role of IRBs in the review of adverse event information from ongoing clinical trials.

Q. *What role should IRBs play in the review of adverse events information from an ongoing clinical trial?*

R. It is my view that IRBs should play no role in the routine review of adverse event reports.

IRBs are not scientific review committees. IRBs are not data/safety monitoring boards. There are limitations on IRB review and committee makeup that make the review of adverse events an activity essentially devoid of utility, including the fact that IRBs receive reports from investigators who often do not know in which arm the adverse event occurred, the numbers of events, the numbers of subjects, and other details critical for taking any reasonable action. If these empty reports are sent to the IRB, however, someone has to do something with them. Thus, IRB resources are expended on reviews with little or no benefit to human subject protection.

Adverse event reports should not be sent to the IRB at all. To clarify, the review and analysis of adverse event reports should occur, just not by the IRB. It doesn't make sense to have adverse events reviewed by a committee of bankers, clergy, psychologists, and social workers.

It is time for the FDA to codify its guidance on the use of the data monitoring committee (DMC) as a subject protection mechanism in clinical trials. Also, the requirement for investigators to develop effective monitoring plans needs to be clearly stated in guidance, if not in regulation. If FDA were to require safety monitoring plans and require DMCs in clinical trials, then the IRB could focus on its required role under the regulations (56.111(a)(6)) and review the plan for monitoring and approve its adequacy for the particular study at hand. Part of that plan should be a description of types of events that will be reported as "unanticipated problems." IRBs currently query investigators about the existence of DMCs, their composition, meeting rules, reporting requirements, etc. The review of the investigator's safety monitoring plan is an appropriate activity for IRBs and helps to ensure that the review of safety reports is accomplished in an effective and timely manner.

Q. *How does that role differ from the current role of IRBs?*

R. IRBs are routinely saddled with the review of any adverse event report that "comes in the front door." A contributing factor to this overload is that any and all adverse events are reported, not just those meeting the three criteria of "serious," "unexpected" and "related" as required in the FDA drug regulations (312.32(c)(1)(i)(A)). Several research institutions have attempted to expressly limit reporting to only those events meeting the FDA criteria. That is, only events that

are related (probably or definitely) and unexpected and serious are to be reported. Often, these policies don't work very well because sponsors and federally funded research bases send all kinds of reports to their investigators and insist that they send them to their IRBs, putting investigators out of compliance if they don't get some review or acknowledgement from the IRB. Again, fear, not efficiency or effectiveness is driving the system. To stop the drain on IRB resources, the flow must stop.

Q. *Should IRB responsibilities for multi-site trials differ from those for single-site trials? If so, how should they differ?*

R. As this question implies, multi-site studies are different from single-site studies in important ways, including the locus of responsibility for protocol design and the oversight of the conduct of the study. The most useless information for IRBs comes from multi-site studies – raw data on multiple adverse event reports from multiple sources. Reviewing these reports is akin to finding a needle in a haystack, while blindfolded and wearing mittens. Despite that IRBs, on rare occasions, have found “needles,” it is counterproductive to insist that valuable IRB time be devoted to this nearly fruitless activity. The same time, spent in more productive ways, would have much greater positive benefit on study design, human safety, and in cooperative relationships between IRBs and investigators. IRBs must be allowed to get out of the business of routinely reviewing adverse event reports regardless of where they occurred.

In 1999, in response to a congressional directive to reduce unnecessary burdens, the NIH issued guidance instructing data safety monitoring boards on NIH-sponsored multi-site trials to forward summary reports of adverse events to each IRB involved in the study. This policy allows processed information from a single source to be considered by the IRB. This is a reasonable approach for multi-site and even single-site studies with such monitoring committees. Routinely, however, NIH-funded research bases for oncology and AIDs violate their own policy and send pages and pages of separate report forms to investigators for forwarding to their IRBs. Unprocessed, unrelated useless points of data.

For single-site studies, the institution and its investigators bear the full responsibility for scientific and subject safety monitoring. An effective system for appropriate study monitoring is an absolute requirement for ethical research, but this is not, and should not be, the job of the IRB. Instead of developing appropriate structures and devoting the additional resources, institutions have tended to dump tasks and responsibilities on the IRB because of their easy availability (to use a phrase from the Belmont Report's description of unjust practices) and because the tendency is to see the IRB as the only responsible party for human subject protection. It is not. IRBs cannot do it all. While the FDA cannot control internal institutional behavior, to the extent that vital human subject protections and regulatory compliance are compromised by these additional burdens, this is a problem for the FDA and the studies they regulate. FDA could mitigate this situation through leadership, guidance and education for research institutions.

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

Q. *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?*

R. As I stated above, IRBs should not routinely review adverse event reports. Adverse event report forms generally do not provide information that IRBs can use effectively and they should not be submitted to IRBs. A summary analysis based upon an event that is 1) related to the study, 2) serious and 3) truly unexpected can provide useful data. Even then, the analysis of the investigator and/or the monitoring function is essential to turn the data into information.

Q. *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)?*

R. The answer to this question seems rather obvious. One of the functions assigned to IRBs is the assessment of risks and ensuring that when modifications are made, the ethical justification is appropriate. The IRB should receive an adverse event summary when it supports a study change (e.g., temporary suspension, termination, change in protocol, consent, recruitment, etc.) and when studies are continued in the face of truly unanticipated problems. An adverse event that is either serious or unexpected might provide part of that justification, depending upon the investigator and/or sponsor assessment. As part of the continuing review process, IRBs must reassess the risks of the study. Summary information about the actual adverse event experience is important to that process, but submitting individual forms or tabular data alone is not very helpful. It is the analysis that is useful.

Q. *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?*

R. The typical adverse event report form does not provide the IRB with useful information even if the event occurred locally. What is useful is an analysis that includes what happened, why the investigator thought it happened and what actions are necessary in light of the occurrence. In a multi-site study, the adverse event report form should be forwarded to the sponsor or the study monitoring committee for an aggregated analysis with other site's report forms, and only the summary of that analysis should be reported back to all reviewing IRBs. For local events that are related and serious and truly unexpected, the local investigator should provide a summary and analysis, based upon the information available, which may well be insufficient for either the investigator or the IRB to take action. The standard for all studies should be that the IRB receives summary information to support actions, not individual adverse event report forms. Information, not data.

Area 3. Approaches to providing adverse events information to IRBs.

Q. *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)?

R. I agree with the consensus statement. As a remedy, IRBs should not be expected or required to receive adverse event reports. As this question implies, it is the information from the events that is useful – this is what needs to be provided. The report forms should be available for audit, further analysis and study documentation, but the IRB should not routinely receive them.

IRBs are not scientific review committees. All IRBs are required to have members who have non-scientific and non-technical backgrounds. Consolidated reports and individual local summary reports should be in narrative format and written in plain language. It would be helpful if the information followed the “5 Ws Rule” of journalistic writing: what happened; when; where; why/how; and what it means or what action will be taken. Including to whom it happened might be appropriate in a unique situation, but generally the IRB does not need such information. If the IRB feels it needs more scientific information or clinical details, however, those always can be requested.

Only consolidated reports should be included as part of the IRB submission for continuing review. Additionally, when a change in the study is requested based upon adverse events, a summary of the events should accompany the request. If the investigator or the sponsor suspends a study because of adverse events, a brief statement of the facts should be provided to the IRB with the notification of the suspension, and a more detailed analysis and recommendations should follow.

Q. *Who should provide such reports?*

R. For single-site studies, the investigator is responsible for conducting and reporting this analysis. If the investigator's study monitoring plan indicates that there is a data monitoring committee, that body should supply the summary report. For multi-site studies, the study sponsor or research base (e.g., cooperative oncology groups, AIDS research networks, etc.) should provide that information, preferably through a data monitoring committee.

Q. *Should the approach to providing IRBs adverse event reports be the same for drugs and devices?*

R. Yes, absolutely. A major source of frustration for IRBs is that different agency regulations require different responses. Even worse, different offices within the same agency interpret requirements differently. Guidance documents provide conflicting advice. Standardization of guidance at the federal level would be a definite improvement and would help promote consistency across research institutions.

To conclude, I wish to restate that reporting unanticipated problems is not the same as sending adverse event report forms. The FDA and HHS could correct the confusion of terms, unrealistic expectations and remedy the situation by issuing clear guidance to sponsors, investigators and IRBs that makes the following points: 1) submitting adverse event report forms to the IRB does not satisfy the FDA's requirement for adverse event reporting – reports are to be submitted to, and analyzed by, sponsors and sponsor-investigators; 2) reports of unanticipated problems (not adverse events reports) to the IRB must include an analysis of the events and recommended actions; 3) adverse event reporting forms sent to IRBs without accompanying analysis should be returned (if original) or destroyed (if copy) without any acknowledgement, review or comment required; 4) sponsors and institutions conducting human subject research should put in place, and support, systems/mechanisms for the ongoing monitoring of studies, e.g., data monitoring committees for clinical trials; and 5) IRBs are not expected to provide continuous monitoring beyond what is required by the continuing review requirements of the current regulations.

Because of concern that other parties may not adequately perform this responsibility, it may be hard for some IRBs to lay down this assumed or imposed burden. It will be harder for investigators and research institutions to establish and support effective systems for monitoring. It may even be difficult for the FDA to redirect adverse event reviews away from IRBs, but unless this is done, the IRB system will struggle and ultimately fail. I thank you for your interest in resolving this complex, but very important, issue and for the opportunity to provide my input into your deliberations and resolution of this long-standing and ever growing problem.