



# University of Pittsburgh

## *Research Conduct and Compliance*

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Division of Dockets Management (HFA-305)  
Food and Drug Administration  
5260 Fishers Lane RM 1061  
Rockville, MD 20852

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

Dear Sir or Madam:

The following comments are being submitted on behalf of the University of Pittsburgh in response to the questions and issues posed in the Food and Drug Administration's Notice of Public Hearing, entitled "Reporting of Adverse Events to Institutional Review Boards", Federal Register, Vol. 70, No. 25, February 8, 21005.

**1. What is or should be the role of IRB's in the review of adverse event information from ongoing clinical trials?**

The primary role of IRBs in their initial and continuing review and approval of the conduct of clinical research studies is the protection of the rights and welfare of the involved research subjects. As outlined in the above-referenced Federal Register notice, to initially approve a proposed clinical investigation, IRBs must determine, among other things, that the risks to the subjects are minimized; the risks are reasonable in relation to anticipated benefits (if any); the selection of subjects is equitable; and the informed consent process is adequate for the anticipated study population and appropriately documented. An IRB's decision whether or not to approve the conduct of a clinical investigation is based on the information available to the IRB at the time its initial review of the research proposal and corresponding materials (e.g., informed consent document).

During the conduct of a clinical investigation, research data related to the safety and/or effectiveness of the experimental intervention will accrue; including information regarding new or previously unobserved or unanticipated adverse events. In order to fulfill their continuing responsibilities for protecting the rights and welfare of research subjects; IRBs must obtain and review this additional adverse event

information so as to determine if the risks to the subjects continue to be minimized, to the extent possible, and if the risks continue to be reasonable in relation to the anticipated benefits (if any) of study participation. For example, should there be additional monitoring of research subjects based on the new adverse event information? Does the new information alter substantially the risk/benefit ratio of study participation so as to warrant a change in eligibility criteria or discontinuation of the clinical investigation? In addition, IRBs must ensure that individuals who are currently participating in the clinical investigation are adequately informed of any information (e.g., new adverse event information) that may affect their decision to continue participation (or, if study participation has been completed, if any follow-up actions are warranted), and that this process and the research subject's decision (whether to continue participation or not) are appropriately documented. If the clinical investigation remains open for additional research subject enrollment, IRBs must also ensure that the informed consent form initially presented to potential research subjects has been appropriately modified to address this new adverse event information.

## **2. What are the types of adverse events about which IRBs should receive information?**

As stated above, in order to fulfill their continuing responsibilities for protecting the rights and welfare of research subjects, IRBs must obtain and review new adverse event information that could potentially alter the risk/benefit ratio of study participation assessed previously by the IRB. IRBs also have responsibility for ensuring that current and future research subjects are informed of any additional adverse event information that could potentially alter or affect their decision to participate in the research study. Upon their initial review of a proposed clinical investigation, IRBs make a decision to approve or disapprove the conduct of the investigation based on the safety (i.e., adverse event) and effectiveness information that exists at the time of this review. Also, the informed consent document initially approved by the IRB is typically inclusive of the adverse event information that is known at the time of this review. Receipt of additional adverse event information that simply supports what was known at the time of the initial IRB review adds negligibly to the IRBs continuing assessment of the risk/benefit ratio of study participation and/or a research subject's decision whether or not to continue study participation. Thus, additional adverse event information received by IRBs during the course of the study should be limited to unanticipated or unexpected adverse events; i.e., adverse events that are not currently identified in the IRB-approved research protocol and informed consent document or adverse events that occur with a greater frequency or severity than described in the current IRB-approved research protocol and informed consent document.

Taking into account the inherent level of risk associated with any clinical investigation involving an article (e.g., investigational drug or device) regulated by the FDA, it is unlikely that new information regarding unanticipated or unexpected adverse events of mild severity would alter an IRB's assessment of the risk/benefit ratio of study participation or a research subject's decision to participate or continue to participate in the clinical investigation. Likewise, the receipt of reports addressing a single, isolated adverse event of possible or questionable relationship to the experimental intervention(s) add minimally to the IRB's or research subject's assessment of the research study or study participation.

Regarding the occurrence of a single, isolated adverse event wherein the relationship to the experimental intervention is not clearly established; this possibility is typically addressed in the informed consent document through the inclusion of general statement such as: "As with any experimental procedure, there may be adverse events or side effects that are currently unknown, and certain of these unknown risks could be permanent, severe, or life-threatening."

The usefulness of adverse event reporting will vary depending on the type of research study undertaken. For multi-center clinical investigations, redundant reports of expected adverse events or reports of isolated adverse events of questionable relationship to the experimental intervention expend limited IRB resources while producing minimal or no increase in research participant safety. In summary, for multi-center clinical investigations, adverse event information that must be provided in a timely manner to responsible IRBs should be focused on consolidated or aggregated reports (see discussion below) of unexpected or unanticipated adverse events of moderate or greater severity that have been observed in multiple research subjects and are felt, based on appropriate medical review, to be definitely or possibly related to the experimental intervention (i.e., a causal relationship between the adverse event and experimental intervention cannot be ruled out). For single-site clinical investigations, adverse event information that must be provided in a timely manner to the responsible local IRB may also include expected serious adverse events; taking into account the institutional risk-management role frequently assumed by the local, institutional IRB.

### **3. What approaches should be used for providing adverse event information to the IRB?**

As addressed in the above-referenced Federal Register notice, adverse event reports submitted individually and sporadically throughout the course of a study without any type of interpretation are ordinarily not sufficiently informative to permit IRBs to assess the implications of reported events for study subjects. Also as presented in this Federal Register notice, an IRB's ability to make useful determinations based on the adverse event information it receives would be improved if, prior to submission, the adverse event reports were consolidated or aggregated and the information analyzed (e.g., a medical assessment of the relationship of the adverse

event to the experimental intervention) and summarized. Additional questions focus on who should be responsible for consolidation and analysis of the adverse event reports and the frequency of submitting the consolidated reports to reviewing IRBs.

The University of Pittsburgh IRB recommends that all clinical investigations submitted for IRB review address a safety and data monitoring plan. This requirement is consistent with the responsibilities of the reviewing IRB as defined under 21 CFR Part 56; i.e., “the research plan, when appropriate, makes adequate provisions for monitoring the data collected to ensure the safety of the human subjects.” This data and safety monitoring plan should address who or what entity will be responsible for the consolidation and analysis of adverse event information prior to its submission to the reviewing IRB(s). For example, this function may be performed by a single individual (e.g., principal investigator or medical director) affiliated with the clinical investigation; a single individual (e.g., medical monitor) not affiliated with the clinical investigation; or a committee (e.g., data and safety monitoring board) affiliated with or independent of the clinical investigation. The data and safety monitoring plan should also address the frequency at which consolidated adverse event reports will be submitted to the reviewing IRB(s). Based on considerations of the nature (single site or multi-center) and risk level of the clinical investigation, the reviewing IRB should determine the adequacy and appropriateness of this data and safety monitoring plan in making its initial decision whether or not to approve the conduct of the research.

Consolidated reports of unexpected adverse events of moderate or greater severity that have been observed in multiple research subjects and are felt, based on appropriate medical review, to be definitely or possibly related to the experimental intervention(s) should be received by reviewing IRBs on no less than a quarterly basis. On an annual basis, either in one of these quarterly reports or in a separate annual data and safety monitoring report, consolidated information regarding unexpected adverse events of mild severity that are felt to be definitely or possibly related to the experimental intervention should also be presented. As part of the annual report, the individual or committee responsible for the consolidation and analysis of the research data should also be required to specifically indicate if, based on the data accrued to date, there is any evidence that the risk/benefit ratio of study participation has been altered (i.e., since the previous annual report).

In conclusion, the University of Pittsburgh IRB welcomes this opportunity to provide input on this important issue regarding research study oversight. In order to carry out their important function of ensuring research participant safety in the face of limited resources, IRBs would welcome useful guidance from the FDA on this topic.

Sincerely,



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