

THE UNIVERSITY OF TEXAS  
MD ANDERSON  
CANCER CENTER

April 15, 2005

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

To Whom It May Concern:

Re: Comments on "Reporting of Adverse Events to Institutional Review Boards"  
Docket No. 2005N-0038

On behalf of the Institutional Review Board and Vice President, Clinical Research at U.T. M.D. Anderson Cancer Center comments for Docket No. 2005N-0038 are attached.

Thank you for the opportunity to comment on this important subject

Sincerely,



Mira D. Shah, CIM  
Manager, Research Compliance

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*A Comprehensive Cancer Center designated by the National Cancer Institute  
located in the Texas Medical Center*

## **Comments on the subject of submission and IRB review of adverse events (AEs)**

The University of Texas M. D. Anderson Cancer Center (UTMDACC) is pleased to take this opportunity to proffer comments on the subject of submission and IRB review of adverse events (AEs). Reporting of AEs is a critical part of all ongoing clinical trials and is vital to the protection of the human subjects on those trials.

The number of protocols submitted to the UTMDACC IRBs has tripled in the last 5 years and the volumes of AEs being submitted have increased accordingly.

### 1. The role of IRBs in the review of AE information from ongoing clinical trials:

The IRBs' primary role in the review of AE information is to ensure that the rights and welfare of human research subjects are protected. To accomplish this goal, each IRB would review all AEs reported for studies where the IRB has been identified as the only IRB to provide oversight of the study or has been identified as the "national" IRB of record.

#### Single-site trials

For a trial being conducted at a single site, the principal investigator (PI) is required to submit any serious/unanticipated AE(s) that a participant experiences. The PI must provide all pertinent information, enabling the IRB members to review all data that may help in the determination of whether the risk to human subjects enrolled on that trial has in any way increased. If the risk is increased, the IRB can determine that the informed consent must be revised and/or that the participant needs to be re-consented as well as provide direction on how the participant will be advised of the new AE(s). The PI is usually in a better position to assess the significance of each AE. Therefore, the reports submitted by the PI should clearly provide details and estimations as to whether the participant is at increased risk or not.

The AEs that are expected, not serious, and unrelated to therapy and which may already be clearly described in the protocol as well as the informed consent document should not be submitted to IRB. Instead, the PI should keep a log of those expected/anticipated AEs, recording the frequency and severity of said events. These should then be submitted to the IRBs during the IRB continuing review process of the trial. The IRB, based on the frequency of occurrence, will then be able to assess whether the risk to the participants has increased or not. The death of any and all participants should be reported to IRB, regardless of the perceived relationship to the therapy. The only exception would be when the study has been defined as one where long term survival is part of the study analysis, the death occurs in the natural course of the disease, and death due to disease is expected in the subject population of the study.

#### Multiple-site trials

If the trial is being conducted at multiple sites, the AEs would be submitted to the national or international PI and the designated IRB of the site at which the PI is employed. The "national" IRB will be able to review a composite of all AEs and data submitted by all participating sites.

This removes the need for each individual site to review the AEs. The aggregate information reviewed in multiple-site trials is a helpful tool for the "national" IRB in assessing the risk to participants on that trial. The national PI would then report back to each of the sub investigators of outcomes of the IRB review. This report would include the following items:

whether or not the event is unexpected (not listed in the protocol and the informed consent)  
whether the event is new or has occurred before  
whether or not the event is related to the treatment and how severe the event is (grading as per the NCI common terminology criteria)

## **2. The types of AEs about which IRBs should receive information:**

Internal (AEs occurring at the institution of record)

The types of internal AEs that IRBs and the sponsor should receive are:

Serious (as per the NCI guidelines or as the protocol document has outlined)  
Unexpected (any event that is not consistent with the current investigator's brochure or the protocol consent document or that is not identified in the body of the protocol as to its nature, severity, or degree of incidence)  
Related or potentially related to study treatment  
Requiring revision to protocol, consent, and/or investigator's brochure

## **3. Approaches to providing AE information to IRBs**

External (AEs that occur at external unaffiliated sites)

Single-site trials

Currently, the sponsor or drug company submits the AE reports to all the other investigators using that particular drug in their studies. The PIs at other sites, in turn, submit the AEs to their respective IRBs. One site may have 5-6 investigators using this same drug, all of whom submit the AEs to their IRB. The volumes created by duplicate reports submitted to IRBs is unnecessary. IRBs should not be required to routinely review external AEs except in instances where the sponsor has made a determination that a revision to the protocol or informed consent document is necessary. The sponsor must revise the investigator brochure and add the AE when such determination is made.

Multiple-site trials

For multi-site studies, the national PI and the IRB for that site should review all AEs for the study where they are considered the "national" IRB for oversight. This includes the AEs that occur at the "national" site of the study as well as those submitted by other sites. The national PI and the IRB at that site would take the responsibility of determining if the protocol and informed

consent document need to be revised. If a change is required, the PI would also inform the sponsor/drug company that a revision to include these additional AEs in the investigator brochure is advised.

For the safety of human subjects involved in clinical research to be protected to the fullest extent possible, the submission of AEs to IRBs for review should be performed in a well-organized and consistent manner. We at UTMDACC thank the FDA for allowing us this opportunity to contribute our comments on this most important subject.