

March 21, 2005

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

Re: Docket # 2005N-0038 Adverse Events Reporting to Investigational Review Boards

Dear Sir or Madam:

As the FDA examines the need for revision of current rules for reporting clinical research adverse events to institutional review boards, the following is shared for your consideration:

I. Role of IRB – The IRB in reviewing unanticipated serious adverse events should carefully assess the relationship of the AE to the research interventions and interactions and determine whether the AE represents an unanticipated problem, requiring reporting in compliance with DHHS regulations. To that end, to what extent should the IRB consider:

1. **Determination of relatedness** – This is pivotal in determining which AEs are reported from sponsors to participating sites, as well as to IRBs for expedited review. However, there are no consistent criteria for attribution determination.
 - a. Whose opinion counts - the sponsor, the external PI, the local PI, or the IRB? Is it the role of the IRB to affirm or confirm the attribution determination? When there is conflict of opinion, is the IRB the final arbiter of the scientific debate?
 - b. Temporal relationship – this consideration appears under-utilized in deciding relatedness. For example, an external, unexpected SAE is reported to a local site with report of a 59 year old subject death within 30 minutes of signing consent and 10 minutes of start of study drug infusion. This is determined to be unrelated by the external PI and the local PI agrees. If the time element is not specifically considered, then most any event in moderate-to-seriously ill subjects may be attributed to other than study participation. This is a concern. It would be helpful to have an attribution category - “temporal relationship only.”
2. **Unblinding:** Review of an SAE is especially difficult in double-blind situations when the blind is not broken. Regulatory conditions for breaking a blind in relation to unexpected SAEs would be helpful, as the protocol frequently leaves this to the discretion of investigator or sponsor. Regulatory backbone consistent with ICH Guideline for Industry Clinical Safety Data Management Definition and Standards for Expedited Reporting (Part III – D, Managing Blinded Therapy Case), would ease this burden.
 - a. **Element of Consent:** it would be helpful if subjects were informed (in the written ICF) the conditions under which unblinding will occur with regard to: (1) completion of active treatment; (2) completion of the trial; (3) new information / interim analysis; and (4) in the event of as unexpected SAE.
3. **Protocol Adherence** – diligent review of unexpected SAEs (internal and external) may require review of the protocol and consent form. Protocol adherence issues may be identified. If protocol adherence is noted by the IRB as a problem contributing to an external SAE – is this reportable?

For example:

- a. In IRB review of 3 similar external, unexpected SAEs (each attributed as unrelated), it was determined that each subject was ineligible.
 - b. It was noted with an external SAE (grade 4 anaphylaxis) that the safety report was an update, and the original was never received by the PI. The coordinating center had failed to send the original to local sites. This is contrary to protocol.
4. **Safety Report Content:** The content of SAE reports vary. It is concerning that some external, unexpected SAE reports are consistently and significantly lacking important information. At the least, this careful parsing of information is a disservice to subjects and at most, it compromises their safety. At times, this may be that the reports are generated prematurely in an effort to notify sites of the SAE occurrence – however, updates are generally late in comparison.
5. **Old Safety Reports:** Not infrequently, later phase trials will be sent safety reports from early trial SAEs that were initially considered unrelated, but through a pharmacovigilance process the attribution is changed to possibly-related. Some of these events are being reviewed by the IRB, 4 and 5 years after they occurred. It would be helpful if safety data was reviewed before the next phase of the trial is underway.
6. **DSMB** – The concept of DSMB is appealing, but their effectiveness and reliability requires ongoing evaluation by the IRB, and certainly does not provide a failsafe mechanism for ensuring participant safety:
- a. Short term trials – industry studies for short duration routinely do not have DSMBs. When these are multi-center studies, local sites may be recruiting 50 or less subjects, and assembling a local DSMB appears impractical in terms of meeting frequency, statistical relevance, etc.
 - b. This IRB suggests that independent DSMBs be required for multi-center trials with greater than low risk.
 - c. Sponsor-provided or internal DSMBs – the potential for conflict of interest is difficult to rule out.
 - d. Unblinded data – should all DSMBs review unblinded data? If not, at what point should this be considered – at a certain level of risk?
 - e. DSMB reports – these reports are rarely substantive, such that relying on them for the purpose of continuing review may not meet regulatory requirement of 45 CFR 46.111. Reports may be limited to noting the date the committee met, and that no changes in the protocol or consent were recommended. If the IRB determines in initial review of a protocol, that the DSMB reviews appropriate information, meets at appropriate frequency, and the protocol has appropriate safety measures, does the IRB need detailed DSMB reports or should they rely that the safety plan is operational as described?

II. Types of Reportable adverse events – It is helpful to receive safety reports for unexpected and serious events occurring with study participation, regardless if they are internal or external. Substantive information regarding the event should be provided to the IRB, including:

- a. An accurate keyword description of the event. Keywords should enhance not impair communication. Keywords often poorly represent (or misrepresent) the SAE. This stymies IRB review. Further, keyword miscommunication is perpetuated when the event is documented in the IB. If the keyword is “off” this may result in filing the event under a different category (thus removing it from juxtaposition to a similar SAE accurately keyworded and housed in the correct category). To the extent keywords do not represent the event, the utility of the investigator brochure is reduced.

- b. a meaningful description of the event, with dates, history of onset (if gradual worsening to serious); lab values; interventions and treatment, present health status
- c. assurance that management of this subject was safe and consistent with protocol, specifically with regard to:
 - 1. eligibility
 - 2. interval safety testing
 - 3. dose reduction
 - 4. stopping rules / discontinuation of study drug
 - 5. unblinding
 - 6. status of subject – withdrawn, terminated, off active tx, etc...
- d. subject age and gender
- e. explanation of how events meets seriousness criteria
- f. concomitant medications
- g. start and stop date of study interventions
- h. significant past medical history and/or comorbidities
- i. PI review and opinion
 - 1. how many other similar events been reported with this drug / intervention?
 - 2. what is the attribution of the event?
 - 3. are consent or protocol changes recommended?
- j. DSMB information – does study have a DSMB, is it internal or external, have they reviewed the event, have regular DSMB reports been received by PI / IRB?

III. Practices of reporting AEs to IRBs - Managing SAEs is resource-intensive from the sponsor, regulatory, investigator and IRB perspectives. Clear and well-communicated local policy along with an infrastructure that supports compliance is necessary. To that end, this institution has developed:

1. an internal, online AE reporting, review and tracking system that is comprehensive, user friendly, and well- suited to the PI's and IRB's purpose of assuring AE compliance.
2. The internal online reporting system directs expedited AEs (meeting local criteria for expedited review) to each of 3 clinical reviewers. At the request of any reviewer, the review of the event may be directed immediately to the IRB or to an IRB-advisory committee that reviews Research Adverse Events on a weekly basis.
3. The advisory committee, the Research Adverse Events Committee, functions in an advisory capacity to the IRB. Members are appointed by the Director of the Human Subjects Protections Office, and represent a multi-disciplinary team of clinicians and researchers.

As noted in the ICH Good Clinical Practice Guidelines 2.3, “The rights, safety and well being of trial subjects are the most important considerations, and should prevail over the interests of science and society.” To satisfy this edict, an effective Adverse Events Reporting System is required.

Sincerely,

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