

DEPARTMENT: Yale University Human Investigation Committee
POLICY NUMBER:
SECTION: Adverse Event Reporting
REVIEW RESPONSIBILITY: IRB Leadership Committee and HIC Policy Review
ORIGINAL CREATION DATE: May 17, 2007

Yale University School of Medicine HIC Policy Regarding: Adverse Event Reporting to the Human Investigation Committee

I. Purpose: The purpose of this policy is to describe how and when investigators should report Adverse Events (AEs) to the Human Investigation Committee (HIC) and other research oversight bodies.

II. Policy Summary

Adverse Events:

Investigators must report to the HIC any Adverse Events that fit the following criteria within 48 hours of discovery:

- a. Serious AND unanticipated AND possibly, probably or definitely related events;
and
- b. Anticipated Adverse Events occurring with a greater frequency than expected

The HIC does not require reporting of any other Adverse Event type.

Reports to the HIC must be in writing using form 6A for reporting AEs under a Yale Principal Investigator (PI). For reporting AEs from external sites under a multicenter research protocol, the investigator must provide aggregated data and an analysis or summary from the sponsor or DSMB, if applicable, sufficient to explain the significance of the event or series of events along with the AE report using form 6B. The forms may be found at: http://www.info.med.yale.edu/hic/forms/forms/form06a_6.11.07_final.doc and http://www.info.med.yale.edu/hic/forms/forms/form06b_6.11.07_final.doc

III. Definitions:

Adverse Event: An undesirable and unintended, although not necessarily unexpected, result of therapy or other intervention.

Unanticipated: Unanticipated events are risks/events which are not cited in the protocol, the consent form or the Investigator's Brochure.

Related: An event is "related" if it is possibly, probably, or definitely caused by the research procedures.

Serious Adverse Event: Any Adverse Event that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or any other Adverse Event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

IV. Guidance

The investigator must evaluate the Adverse Event and determine whether the Adverse Event affects the Risk/Benefit ratio of participating in the study and whether modifications to the protocol (*at Protection of Research Subjects; Risks, Minimizing Risks, or in Procedures*) and/or the consent form (*at Risks and Inconveniences*) are required. If so, an Adverse Event form (form 6A) and an amendment should be submitted promptly to the HIC.

For multicenter studies the investigator must submit a report which provides aggregated data and an analysis or summary explaining the significance of the Adverse Event or series of events in order to ensure the information is interpretable and relevant to the HIC's task of protecting the rights and welfare of human subjects. The HIC recognizes that the sponsor, because it receives Adverse Event information from all study sites, is in a better position to process and analyze the significance of Adverse Event information. Therefore, an investigator may rely on the sponsor's assessment and provide to the HIC a report prepared by the sponsor or DSMB, if applicable. The report should evaluate the event and make a determination as to whether the Adverse Event affects the Risk/Benefit ratio of participating in the study and whether modifications to the protocol and/or consent form are required. If so, the Adverse Event form (form 6B) and an amendment should be submitted promptly to the HIC.

Examples of Adverse Events that are reportable as Serious Adverse Events include:

- Any adverse experience that, even without detailed analysis, represents a serious unexpected Adverse Event that is rare in the absence of drug exposure (such as agranulocytosis, hepatic necrosis, Stevens-Johnson syndrome).
- A series of Adverse Events that, on analysis, is both unanticipated and a problem for the study. There would be a determination that the series of Adverse Events represents a signal that the Adverse Events were not just isolated occurrences and were significant to the rights and welfare of subjects. A summary and analyses supporting the conclusion must accompany the report.
- An Adverse Event that is described or addressed in the investigator's brochure, protocol, or informed consent documents, or expected to occur in study subjects at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in subject population), but that occurs at a greater

frequency or at greater severity than expected. A discussion of the divergence from expected rates must accompany the report.

- Any other Adverse Event that would cause the sponsor to modify the investigator's brochure, study protocol, or informed consent documents, or would prompt other action by the HIC to assure the protection of human subjects. An explanation of the conclusion must accompany the report.

Principal investigators and sponsors have additional reporting responsibilities (e.g., FDA, OHRP), as stated in federal regulations and contractual agreements. This policy does not affect those responsibilities.

V. Background

The rationale for reporting Adverse Events to the HIC is to enable the HIC to fulfill its role of oversight for protection of human subjects. Per federal regulation (21 CFR 56.108(b)(1) (FDA) and 45 CFR 46.103.b.5 (HHS)), the HIC is required to follow written procedures for insuring prompt reporting to the HIC of any serious unanticipated Adverse Events or unanticipated problems involving risks to subjects and others.

More information on reporting Unanticipated Problems Involving Risks to Subjects or Others can be found at: <http://info.med.yale.edu/hic/policy/index.html>

By reviewing reports of certain types of Adverse Events that may impact the subjects' welfare, the HIC can require investigators to think about and implement subject protections. Consideration should involve assessing whether there has been a change to the risk/benefit ratio, assessing whether changes are required to the protocol or procedures in order to minimize risks, and deciding whether changes are required in the information shared with current, potential, and previously enrolled subjects (as reflected in the consent form).

Comprehensive data collection about any and all Adverse Events that occur in human research is mandatory. Such data need to be (and are) routinely collected by study personnel, and routinely reported to the sponsor. The sponsor then may have obligations to report such data to regulatory agencies (such as the FDA in cases where drugs are involved). The sponsor also has obligations to keep investigators updated in terms of any new information and therefore will forward reports of Adverse Events to all principal investigators. Often, these reports come with a request or demand to forward such reports to the local IRB. Thus, the report is often submitted to the IRB per the request of the sponsor whether or not the given report meets the local IRB's standards for reporting. However, the HIC will not accept AE reports unless the event meets the criteria defined above. All reports failing to meet the criteria will be returned to the investigator.

An Adverse Event can be analyzed from many perspectives:

- The nature of the event (or the grade) such as "serious" versus "non-serious" or grades 1 through 3, where 1 is mild and 3 is severe. The various grades

appropriate to the given protocol must be defined in advance, with particular attention placed on the definition of “serious.” Serious events can encompass physical, psychological, social, legal, and economic harm, harm to dignity, and unexpected threats to privacy or safety. When applied to a protocol involving drugs, “serious” by FDA definition encompasses any adverse experience resulting in death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect, or any other Adverse Event that, based upon appropriate medical judgment, may jeopardize the subject’s health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

- The “expectedness” of the event; that is, was the event anticipated or unanticipated at the time of study design? Does the event suggest that the research places subjects at greater risk of harm than was previously known or recognized? Did the frequency of anticipated, related events exceed expectations? Anticipated events should be listed as potential risks in the protocol and the consent form.
- The “relationship” of the event to the study; that is, did the procedure or intervention used in research reasonably cause the event? The concept of relatedness is often thought of in terms of degree, such as, unrelated; or unlikely to be, possibly, probably, or definitely related.

For more information regarding the attribution and grading of Adverse Events, see the DSMP policy. <http://info.med.yale.edu/hic/templates/dsmp.doc>

References

Morse MA, Califf, RM and Sugarman, J: Monitoring and ensuring safety during clinical research, JAMA 2001; 285:1201-1205

FDA regulations: 21CFR56.108.b and 113

DHHS regulations: 45CFR46.103.b.5

Links:

<http://info.med.yale.edu/hic/policy/dsmp.pdf>

http://info.med.yale.edu/hic/policy/protocol_deviations.pdf

<http://www.hhs.gov/ohrp/policy/AdvEvtGuid.htm>