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# Yale University Institutional Review Boards

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## 710 PR.1 Reporting Adverse Events to the IRB

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### Overview

This procedure describes the process whereby certain types of adverse events are reported to the IRB by the Yale principal investigator.

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### Format of Adverse Event Reports

Reports to the IRB must be in writing using Form 710 FR1 for reporting serious, unanticipated and possibly related adverse events (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 Data Safety Monitoring Board (DSMB), when applicable and available, sufficient to explain the significance of the event or series of events along with the AE report using Form 710 FR1 and Form 710 FR.2. The forms may be found at: <http://www.yale.edu/hrpp/forms/> and <http://www.yale.edu/hrpp/forms/>. For AEs that don't qualify as serious, unanticipated or possibly related, a brief summary may be included in the renewal application. It is sufficient for the summary to be a simple brief statement that adverse events have occurred at the expected frequency and level of severity as previously documented.

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 it to them. However, the Yale IRB neither requires nor accepts AE reports unless the event meets the criteria defined in Policy 700: Protocol Deviations and Noncompliance. All reports failing to meet the criteria will be returned to the investigator.

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### Examples of Adverse Events Reportable as Serious Adverse Events

- 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 significantly affected the rights and welfare of participants. A summary and analysis 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 participants at an anticipated rate (e.g., expected progression of disease, occurrence of events consistent with background rate in participant 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 IRB to assure the protection of human participants. An explanation of the conclusion must accompany the report.

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## Investigator Evaluation of Adverse Events

The investigator must evaluate the adverse event and determine whether or not the adverse event affects the risk/benefit ratio of participating in the study and whether or not modifications to the protocol and/or the consent form are required. For example the Investigator may consider suspending the protocol pending further review, notification of current or past participants, or changes to participant monitoring plans. If so, an adverse event form and an amendment request should be submitted promptly to the IRB.

For multicenter studies the Yale 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 IRB’s task of protecting the rights and welfare of human participants. The IRB 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 IRB a report prepared by the sponsor or DSMB, if applicable and when available. 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 and an amendment request should be submitted promptly to the IRB.

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## Evaluation Considerations

Reviewing reports of certain types of adverse events that may impact the participants’ welfare, requires investigators to think about and implement participant 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).

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 participant’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 participants 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, and their likelihood of occurrence indicated in an understandable way (e.g. x number out of 100).
- 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.

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## 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://yale.edu/hrpp/policy/dsmp>

[http://yale.edu/hrpp/policy/protocol\\_deviations](http://yale.edu/hrpp/policy/protocol_deviations)

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