IRB Adverse Event Guidance

What are unanticipated problems?[1]

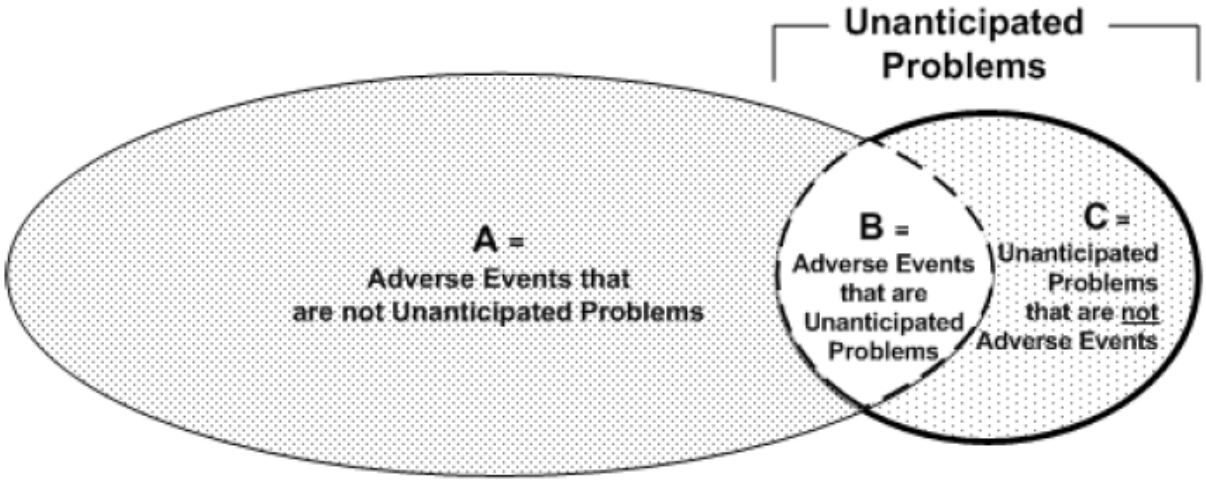
The phrase "unanticipated problems involving risks to subjects or others" is found but not defined in the HHS regulations at 45 CFR part 46. OHRP considers unanticipated problems, in general, to include any incident, experience, or outcome that meets **all** of the following criteria:

(1) unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

(2) related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

(3) suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

The following Venn diagram summarizes the general relationship between adverse events and unanticipated problems:

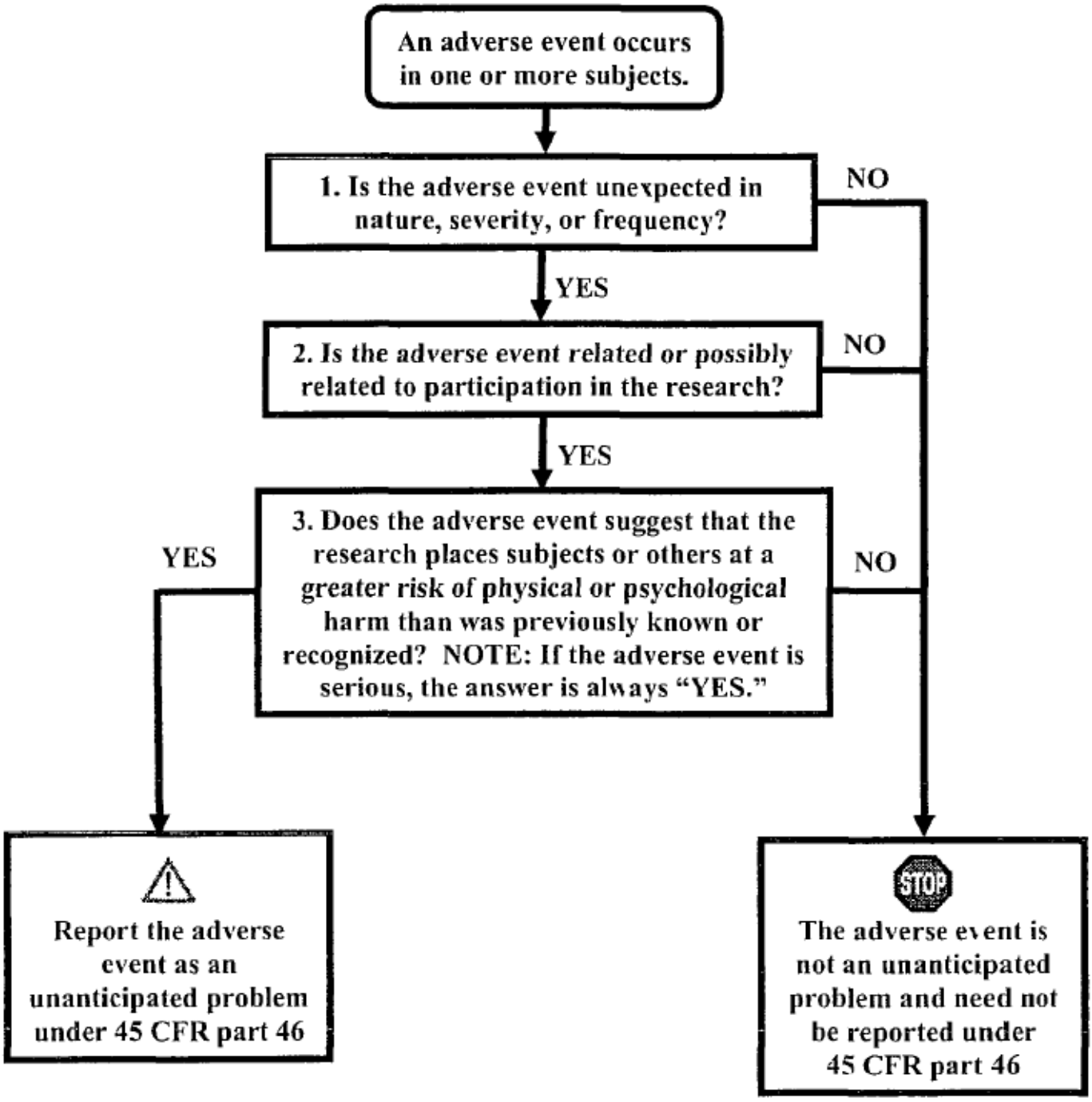


Under 45 CFR part 46: Do not report A; Report B and C.

The key question regarding a particular adverse event is whether it meets the three criteria described in section I and therefore represents an unanticipated problem.

To determine whether an adverse event is an unanticipated problem, follow the algorithm:

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem



How to Determine If an AE is an Unanticipated Problem that Needs to Be Reported?[2]

FDA believes that only the following AEs should be considered as *unanticipated problems* that must be reported to the IRB.

- A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure (such as angiodema, agranulocytosis, hepatic injury, or Stevens-Johnson syndrome).

- A single occurrence, or more often a small number of occurrences, of a serious, unexpected event that is not commonly associated with drug exposure, but uncommon in the study population (e.g., tendon rupture, progressive multifocal leukoencephalopathy).

- Multiple occurrences of an AE that, based on an aggregate analysis, is determined to be an unanticipated problem. There should be a determination that the series of AEs represents a signal that the AEs were not just isolated occurrences and involve risk to human subjects (e.g., a comparison of rates across treatment groups reveals higher rate in the drug treatment arm versus a control). We recommend that a summary and analyses supporting the determination accompany the report.

- An AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but occurs at a specificity or severity that is inconsistent with prior observations. For example, if transaminase elevation is listed in the investigator's brochure and hepatic necrosis is observed in study subjects, hepatic necrosis would be considered an unanticipated problem involving risk to human subjects. We recommend that a discussion of the divergence from the expected specificity or severity accompany the report.

- A serious AE that is described or addressed in the investigator's brochure, protocol, or informed consent documents, but for which the rate of occurrence in the study represents a clinically significant increase in the expected rate of occurrence (ordinarily, reporting would only be triggered if there were a credible baseline rate for comparison). We recommend that a discussion of the divergence from the expected rate accompany the report.

- Any other AE or safety finding (e.g., based on animal or epidemiologic data) 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 ensure the protection of human subjects. We recommend that an explanation of the conclusion accompany the report.

REPORTING AEs TO IRBs IN CLINICAL TRIALS OF DEVICES UNDER THE IDE REGULATIONS

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3(s)). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor and the reviewing IRB as soon as possible, but in no event later than 10 working days after the investigator first learns of the event (§ 812.150(a)(1)).

- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (§§ 812.46(b), 812.150(b)(1)).

CONCLUSION

The receipt of a large volume of individual AE reports without analysis of their significance to a clinical trial rarely supports an IRB's efforts to ensure human subject protection. Sponsors can assess the implications and significance of AE reports promptly and are required to report serious, unexpected events associated with the use of a drug or device, including analyses of such events, to investigators and to FDA. In addition, sponsors are required to report analyses of unexpected adverse device experiences to IRBs. FDA encourages efforts by investigators and sponsors to ensure that IRBs receive meaningful AE information. The ultimate goal is to provide more meaningful information to IRBs, particularly when sponsor analysis (including an analysis of the significance of the adverse event, with a discussion of previous similar events where appropriate) is made available to IRBs.

Please contact the IRB Manager, at (206) 341-0787 if you have questions.

Compiled from the following sources:

[1] Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, January 2007.

[2] Guidance for Clinical Investigators, Sponsors, and IRBs, Adverse Event Reporting to IRBs —Improving Human Subject Protection, January 2009.