

Requirements for Notifying the IRB of Unanticipated Problems and Adverse Events

This policy applies to all non-exempt human subjects research conducted by Upstate Medical University faculty. The purpose of this policy is to ensure the prompt reporting of unanticipated problems and adverse events to the IRB, so that human subjects can be better protected from avoidable harms. It should be noted that only a small subset of adverse events occurring in research subjects are unanticipated problems that must be reported to the IRB.

I. **Unanticipated Problems** includes any incident, experience, or outcome that meets **all** of the following criteria:

- A. 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;
- B. related or possibly related to participation in the research (*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
- C. 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.

II. Adverse Events:

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

Includes both physical & psychological harms

A serious adverse event *is* any untoward medical occurrence that:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- results in inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- 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

III. Reporting Internal Adverse Events by Investigators to the Upstate IRB:

- **Internal adverse events** are those adverse events experienced by subjects enrolled by investigators at Upstate or enrolled by affiliated investigators at other institutions for which the Upstate IRB is responsible.

Upon becoming aware of an adverse event, the investigator must first determine whether or not the adverse event meets the criteria for an unanticipated problem (as described in section I). If the adverse event is determined to be an unanticipated problem, it must be promptly reported to the Upstate IRB.

Please Note: when making the determination as to whether the adverse event meets the 1st criterion “unexpected”, consider the known or foreseeable risks (that are described in the protocol, IB, product labeling, package inserts, and consent form) **AND** the expected natural progression of any underlying disease, disorder or condition of the subject and the subject’s predisposing risk factor profile for the adverse event.

If the adverse event is not consistent with either the known or foreseeable risks or subject profile (as described above), then it would be consider “unexpected”.

IV. Reporting External Adverse Events by Investigators to the Upstate IRB:

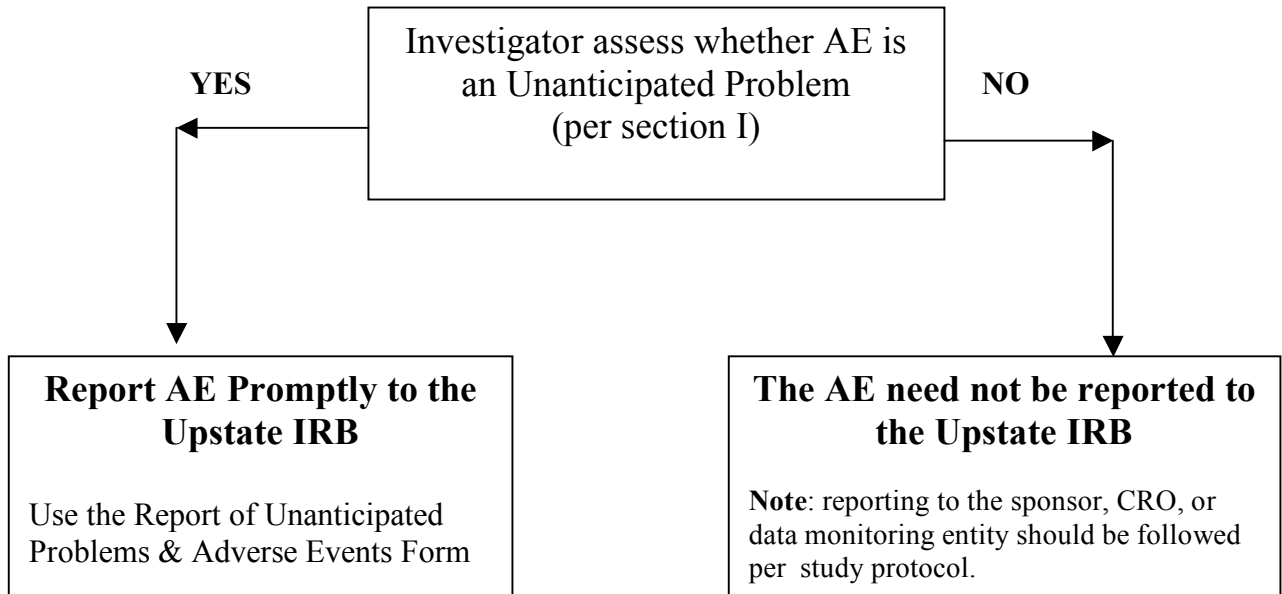
- **External Events** are those adverse events experienced by subjects enrolled by investigators at other institutions engaged in the research.

In multicenter trials neither the investigator nor the IRB will be able to appropriately assess the significance of the external adverse event.

Per OHRP guidance: Individual adverse events should only be reported to all the investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an unanticipated problem.

Therefore only adverse events which have been determined to meet the criteria for an Unanticipated Problem need to be reported to the Upstate IRB. The investigator may need additional information from the monitoring entity (i.e., sponsor, DSMB, statistical center) to make this determination.

Determining when an internal or external adverse event requires reporting to the IRB:



****Note:** if the investigator initially determines that an adverse event is NOT an unanticipated problem, but the monitoring entity subsequently determines that the adverse event does in fact represent an **unanticipated problem**, then the investigator should report this to the IRB.*

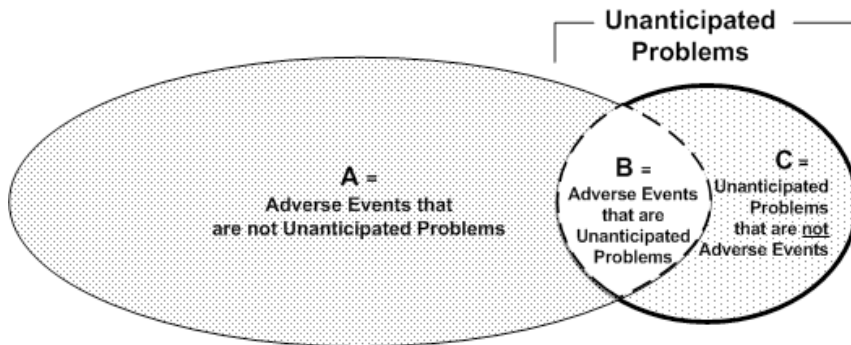
OHRP considers adverse events that are unexpected, related or possibly related to participation in research, and *serious* to be the most important subset of adverse events representing unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized and routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects.

However, other adverse events that are unexpected and related or possibly related to participation in the research, but *not* serious, would also be unanticipated problems if they suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. Again, such events routinely warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

V. Reporting Unanticipated Problems (not related to Adverse Events) to the Upstate IRB:

Upon becoming aware of any other incident, experience or outcome, the investigator must first determine whether or not the incident, experience or outcome represents an unanticipated problem (as described in section I). If the incident, experience or outcome is determined to be an unanticipated problem, it must be promptly reported to the Upstate IRB.

Adverse Events Vs. Unanticipated Problems



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

Note:

- The vast majority of adverse events occurring in human subjects are not unanticipated problems (area A).
- A small proportion of adverse events are unanticipated problems (area B).
- Unanticipated problems include other incidents, experiences, and outcomes that are not adverse events (area C).

VI. Time-Frame for investigators to report ALL Unanticipated Problems (including unanticipated adverse events) to the IRB

In order to ensure that appropriate steps are taken in a timely manner to protect other subjects from avoidable harm, the IRB expects investigators to promptly report Unanticipated Problems to the IRB, as follows:

1. **Unanticipated Problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.**
2. **Any other Unanticipated Problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.**

VII. IRB Review of Unanticipated Problems Reported by Investigators

Reports of *internal unanticipated problems* will be initially screened by the IRB Chair, Vice Chair or IRB administrator to determine if any immediate action is required to protect the safety, welfare, or rights of subjects or others. All internal reports of unanticipated problems submitted by investigators to the IRB will be added to the next open IRB meeting agenda to be reviewed during a convened meeting of the IRB.

Reports of *external unanticipated problems* will be reviewed by the IRB Chair, Vice Chair or other experienced IRB member to determine if any additional action is required.

It is expected that reports of unanticipated problems may warrant consideration of substantive changes in the research protocol or informed consent process or document. The following are examples of corrective actions or changes the IRB or designated IRB member may consider in response to an unanticipated problem:

- Modification of the eligibility criteria;
- Implementation of additional monitoring procedures;
- Modification of informed consent documents;
- Provision of additional information to previously enrolled subjects;
- Suspension of enrollment of new subjects;
- Suspension of research procedure in currently enrolled subjects;
- Termination of approval of research

VIII. IRB Reporting to Institutional Official, HHS supporting agency head, OHRP and FDA

OHRP and FDA regulations require that Upstate notify institutional officials, supporting HHS agency heads, OHRP and FDA (if applicable) of all internal unanticipated problems. These reports do not indicate any deviation or wrong doing on the part of the investigators; but, instead, are made to inform federal agencies of potential changes in risk in previously-approved research due to *unanticipated problems*.

The IRB administrator or IRB coordinator will report all **internal unanticipated problems** to the Upstate Vice President for Research, HHS supporting agency head (if applicable), OHRP and FDA (if applicable) within one month of the IRB's receipt of the report of the problem from the investigator. The IRB provides copies of these reports to the PI.

Algorithm for Determining Whether an Adverse Event is an Unanticipated Problem

