

Clinical Research Definitions and Procedures

Steven Hirschfeld MD PhD
Associate Director for Clinical Research
National Institute of Child Health and Human Development

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health



National Institute of
Child Health and Human
Development (NICHD)

Abbreviations

- CFR= Code of Federal Regulations
- DHHS= Department of Health and Human Services
- FDA= Food and Drug Administration
- ICH= International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
- IDE= Investigational Device Exemption from FDA
- IND= Investigational New Drug Application from FDA
- IRB= Institutional Review Board
- OHRP= Office for Human Research Protection of DHHS
- NIH= National Institutes of Health
- WHO= World Health Organization

What is research?

Department of Health and Human Services (DHHS) regulations define **research** at 45 CFR 46.102(d) as follows:

Research means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities.

Definition of Human Subject in Research

The DHHS regulations "Protection of Human Subjects" 45 CFR Part 46, administered by the Office for Human Research Protection (OHRP), define a ***human subject*** as a living individual about whom an ***investigator*** conducting ***research obtains***:

- Data through ***intervention*** or ***interaction*** with the individual or
- ***Identifiable private information***

Definition of Investigator

- ***Investigator.*** The OHRP considers the term investigator to include anyone involved in conducting the research. OHRP does not consider the act of solely providing coded private information or specimens (for example, by a tissue repository) to constitute involvement in the conduct of the research. However, if the individuals who provide ***coded*** information or specimens also collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, they will be considered to be involved in the conduct of the research (OHRP's Coded Specimen Guidance).

Definition of Obtains

- ***Obtains.*** In its guidance for use of coded specimens, OHRP has determined that under the definition of human subject at 45 CFR 46.102(f), ***obtaining*** identifiable private information or identifiable specimens for research purposes constitutes human subjects research. ***Obtaining*** means receiving or accessing identifiable private information or identifiable specimens for research purposes. OHRP interprets ***obtaining*** to include an investigator's use, study, or analysis for research purposes of ***identifiable private information*** or identifiable specimens already in the possession of the investigator.

Definitions of intervention and interaction

- ***Intervention*** includes both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes (45 CFR 46.102(f)).
- ***Interaction*** includes communication or interpersonal contact between investigator and subject (45 CFR 46.102(f)).

Definition of private information

- ***Private Information*** includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (for example, a medical record). Private information must be ***individually identifiable*** (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (45 CFR 46.102(f)).

Definition of identifiable private information

- ***Individually Identifiable Private Information.***
According to its guidance for use of coded specimens, OHRP generally considers private information or specimens to be ***individually identifiable*** as defined at 45 CFR 46.102(f) when they can be linked to specific individuals by the investigator(s) either directly or indirectly through ***coding*** systems. Conversely, OHRP considers private information or specimens not to be individually identifiable when they cannot be linked to specific individuals by the investigator(s) either directly or indirectly through coding systems.

What is clinical research?

Conceptual Definition: Clinical research is research that either directly involves individual people or uses materials of human origin, such as observed behavior, answers to questions or tissue samples, obtained through direct contact with a particular living person that volunteers and agrees to participate in a research study.

Formal NIH Definition of Clinical Research

NIH defines human clinical research as:

- (1) Patient-oriented research. Research conducted with human subjects (or on material of human origin such as tissues, specimens and cognitive phenomena) for which an investigator (or colleague) directly interacts with human subjects. Excluded from this definition are *in vitro* studies that utilize human tissues that cannot be linked to a living individual. Patient-oriented research includes:
 - (a) mechanisms of human disease,
 - (b) therapeutic interventions,
 - (c) clinical trials, or
 - (d) development of new technologies.
- (2) Epidemiologic and behavioral studies.
- (3) Outcomes research and health services research.

http://grants.nih.gov/grants/funding/phs398/instructions2/p2_human_subjects_definitions.htm

What is a clinical trial?

Conceptual Definition: Clinical trials are clinical research studies to determine whether biomedical or behavioral interventions are safe, efficacious, and effective.

Formal NIH Definition of Clinical Trial

The NIH defines a ***clinical trial*** as a prospective biomedical or behavioral research study of human subjects that is designed to answer specific questions about biomedical or behavioral interventions (drugs, treatments, devices, or new ways of using known drugs, treatments, or devices). Clinical trials are used to determine whether new biomedical or behavioral interventions are safe, efficacious, and effective. Behavioral human subjects research involving an intervention to modify behavior (diet, physical activity, cognitive therapy, etc.) fits this definition of a clinical trial. Human subjects research to develop or evaluate clinical laboratory tests (e.g. imaging or molecular diagnostic tests) might be considered to be a clinical trial if the test will be used for medical decision making for the subject or the test itself imposes more than minimal risk for subjects. Biomedical clinical trials of experimental drug, treatment, device or behavioral intervention may proceed through four phases

Applicable Regulations

- Federally funded research is subject to regulations from the OHRP in Title 45 of the Code of Federal Regulations (CFR)
- Research using products either approved by the Food and Drug Administration (FDA) for interstate commerce or under an Investigational Drug Application (IND) or Investigational Device Exemption (IDE) from the FDA are subject to regulations in Title 21 of the CFR

Adverse Event Reporting

- FDA and OHRP have different regulations and different criteria for reporting adverse events
- The major differences are in the definitions of events that would require an expedited report, the timing of reporting, and to whom the reports are sent

Differences in definitions

- OHRP uses the concept of “unanticipated problem”
- FDA uses the concept of “adverse drug experience”

Reporting of unanticipated problems to OHRP

- Institutions engaged in human subjects research conducted or supported by DHHS must have written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and any supporting department or agency head of any ***unanticipated problem*** involving risks to subjects or others (45 CFR 46.103(b)(5)).
- For research covered by an assurance approved for federalwide use by OHRP, DHHS regulations at 45 CFR 46.103(a) require that institutions promptly report any unanticipated problems to OHRP.

Unanticipated Problems-OHRP

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:

- **unexpected**
- **related or possibly related to participation in the research**
- 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.

Adverse Events-OHRP

- The DHHS regulations at 45 CFR part 46 do not define or use the term *adverse event*, nor is there a common definition of this term across government and non-government entities.
- OHRP uses the term *adverse event* very broadly and includes any event meeting the following definition:
 - 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*

Rationale-OHRP

- 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

Unexpected-OHRP

Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either:

- the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or
- the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

(Modified from the definition of *unexpected adverse drug experience* in FDA regulations at 21 CFR 312.32(a).)

Relatedness-OHRP

Assessing whether an adverse event is *related or possibly related to participation in research*

Adverse events may be caused by one or more of the following:

- (1) the procedures involved in the research;
- (2) an underlying disease, disorder, or condition of the subject; or
- (3) other circumstances unrelated to either the research or any underlying disease, disorder, or condition of the subject.

In general, adverse events that are determined to be at least partially caused by (1) would be considered related to participation in the research, whereas adverse events determined to be **solely** caused by (2) or (3) would be considered unrelated to participation in the research.

Caveats on Relatedness-OHRP

- OHRP recognizes that it may be difficult to determine whether a particular adverse event is related or possibly related to participation in the research.
- Many individual adverse events occurring in the context of research are not related to participation in the research and, therefore, do not meet the second criterion for an unanticipated problem and do not need to be reported under the DHHS regulations 45 CFR part 46.103(a) and 46.103(b)(5)

Seriousness-OHRP

OHRP defines *serious adverse event* as any adverse event 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 (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

IRB Actions-OHRP

- OHRP notes that IRBs have authority to suspend or terminate approval of research that, among other things, has been associated with unexpected serious harm to subjects (45 CFR 46.113). In order for IRBs to exercise this important authority in a timely manner, they must be informed promptly of those adverse events that are unexpected, related or possibly related to participation in the research, and serious (45 CFR 46.103(b)(5)).

Unexpected but not serious-OHRP

- 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.
- 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

OHRP Reporting

- Unanticipated problems that are serious adverse events should be reported to the IRB within 1 week of the investigator becoming aware of the event.
- Any other unanticipated problem should be reported to the IRB within 2 weeks of the investigator becoming aware of the problem.
- All unanticipated problems should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

Safety review for investigational product and marketed product under IND-FDA

The sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the sponsor from any source, foreign or domestic, including

- information derived from any clinical or epidemiological investigations,
- animal investigations,
- commercial marketing experience,
- reports in the scientific literature, and
- unpublished scientific papers, as well as
- reports from foreign regulatory authorities that have not already been previously reported to the agency by the sponsor

21CFR312.32(b)

Exemption from IND reporting for off study use of a **marketed drug-FDA**

- A sponsor of an IND clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.
- The responsibility for reporting is with the license holder

Safety Review for Marketed Product-FDA

Each applicant shall promptly review all adverse drug experience information obtained or otherwise received by the applicant from any source, foreign or domestic, including information derived from

- commercial marketing experience,
- postmarketing clinical investigations,
- postmarketing epidemiological/surveillance studies,
- reports in the scientific literature
- unpublished scientific papers

Expedited Reporting- FDA

- IND-
 - Any adverse experience associated with the use of the drug that is both serious and unexpected or
 - Any finding from tests in laboratory animals that suggests a significant risk for human subjects
- Marketed Product-The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic

Adverse Event-FDA

- Adverse event is used but not explicitly defined in 21 CFR
- Adverse event is defined in FDA Guidance based on the definitions in ICH E2A
“Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.”

Adverse Drug Experience-FDA

Adverse experience. Any adverse event associated with the use of a biological or drug in humans, whether or not considered product or drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; an adverse event occurring from drug overdose whether accidental or intentional; an adverse event occurring from drug abuse; an adverse event occurring from drug withdrawal; and any failure of expected pharmacological action.

21CFR 310.305, 314.80, and 600.80

Adverse Drug Event- Other Definitions

- Investigational Agent-all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. (ICH E 2A)
- Marketed Product-A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function. (WHO Technical Report 498 [1972])

Serious Adverse Drug Experience- FDA

- *Serious adverse drug experience*: Any adverse drug experience occurring at any dose that results in any of the following outcomes:
- Death,
- a life-threatening adverse drug experience,
- inpatient hospitalization or prolongation of existing hospitalization,
- a persistent or significant disability/incapacity,
- a congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

21CFR312.32 & 314.80

Examples of serious events-FDA

- Allergic bronchospasm requiring intensive treatment in an emergency room or at home,
- Blood dyscrasias or convulsions that do not result in inpatient hospitalization,
- Development of drug dependency or drug abuse.

Life threatening experience-FDA

- *Life-threatening adverse drug experience.* Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

IND unexpected experience-FDA

- *Unexpected adverse drug experience*: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.

Unexpected Experience Examples- FDA

- Hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis.
- Cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents.

Adverse Experience-Licensed Product

Any adverse experience that is not listed in the current labeling for the product. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the event because of greater severity or specificity.

Associated with the use of-FDA

- IND- There is a reasonable possibility that the experience may have been caused by the drug.
 - As a matter of policy, serious adverse events that occur within 30 days of administration of the last dose of the product are generally interpreted as associated with the use of
- Marketed Product- Does not apply

21CFR312.32(a)

IND Expedited Reporting Time Frame-FDA

- Each notification shall be made as soon as possible and in no event later than 15 calendar days after the sponsor's initial receipt of the information.

However

- any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than 7 calendar days after the sponsor's initial receipt of the information.

21CFR312.32(c)

IND Delayed Recognition-FDA

- If the results of a sponsor's investigation show that an adverse drug experience not initially determined to be reportable under expedited reporting is so reportable, the sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.

21CFR312.32(d)(3)

FDA Postmarketing Expedited Reporting

- *Postmarketing "Alert reports"*. The applicant shall report each adverse drug experience that is both serious and unexpected, whether foreign or domestic, as soon as possible but in no case later than 15 calendar days of initial receipt of the information by the applicant.
- Follow up reports also have 15 day due date

Marketed Product Literature Reports-FDA

A 15-day Alert report based on information from the scientific literature (found in scientific and medical journals either as case reports or as the result of a formal clinical trial) on serious and unexpected adverse drug experiences is required to be accompanied by a copy of the published article.

IND Periodic Reporting-FDA

Results of a sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.

21CFR312.32(d)(4)

FDA Post Marketing Periodic Reporting

The applicant shall report each adverse drug experience not reported as an expedited report:

- quarterly intervals, for 3 years from the date of approval of the application, and
 - then at annual intervals.
- Periodic reporting, except for information regarding 15-day Alert reports, does not apply to
 - adverse drug experience information obtained from postmarketing studies (whether or not conducted under an investigational new drug application),
 - from reports in the scientific literature, and
 - from foreign marketing experience.

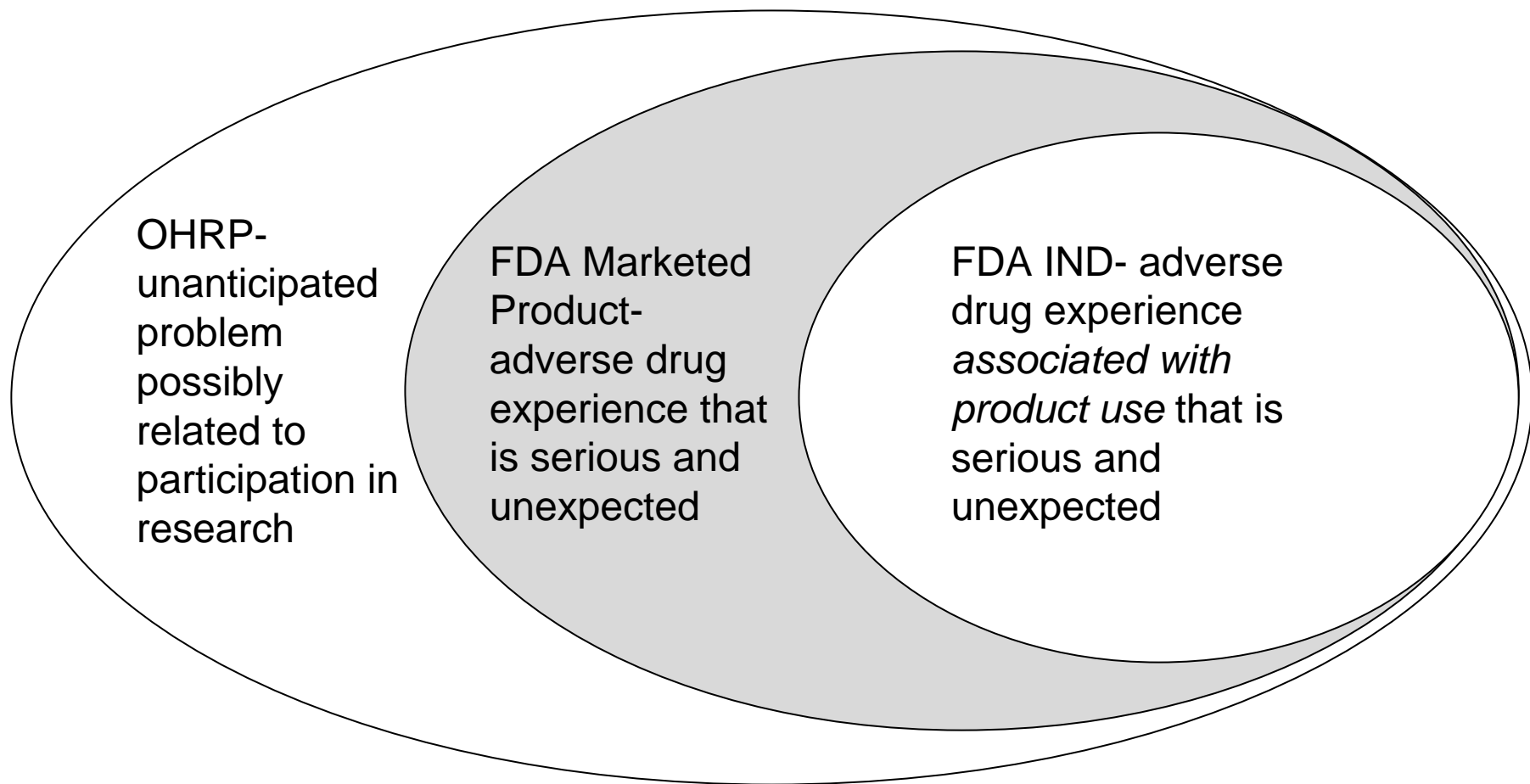
21CFR314.80(c)

Disclaimer Allowed by FDA

A safety report or other information submitted by a sponsor or applicant (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the sponsor or applicant or FDA that the report or information constitutes an admission that the product caused or contributed to an adverse experience. A sponsor need not admit, and may deny, that the report or information submitted by the sponsor constitutes an admission that the product caused or contributed to an adverse experience.

Based on 21CFR312.32(e) and 21CFR314.80(k)

Comparison of OHRP and FDA Expedited Reporting Expectations



Comparison

- OHRP and FDA are both human protection (risk assessment) oriented
- OHRP safety reporting is based upon participation in research
- FDA safety reporting is product oriented and based upon use of the product
- Consistency and harmonization exist for the definition of serious adverse event

OHRP- Unanticipated problem	FDA IND- Adverse product experience	FDA Marketed- Adverse product experience
Unexpected based on protocol related documents or natural progression of disease or condition	Unexpected based on investigator's brochure or protocol	Unexpected based on approved package insert
Possibly related	Associated with the use of	
Greater risk of harm than was previously known or recognized	Serious	Serious
To IRB If serious adverse event- within 1 week Other unanticipated problem- within 2 weeks To OHRP and others- within one month	To FDA and all participating investigators Fatal or life threatening- within 7 days Other-within 15 days	To FDA and others named in product label Within 15 days

The Common Theme

- All expedited reporting requirements are based on “unexpected” events

Recommendation

To clarify what is an **expected event**, insert into the study protocol (even if described in other documents):

- A description of the safety profile for **each** product administered in a study (investigational and marketed)
- A description of the scope of expected adverse events of the underlying condition based on either a recent literature review or textbook
- Consider a composite listing of adverse events that may occur on study noting frequency, severity and duration

Potential Uses of a Composite Listing of Expected Adverse Events

- Assist Institutional Review Board and others in determining overall risks of study
- Assist the process of Informed Consent
- Guide investigators in determining the need for expedited reporting

Recommendation

- Employ similar criteria for reporting to the IRB, OHRP and FDA
- All events that are unexpected and serious are reported
- Unexpected adverse events associated with study procedures that are not part of routine care should also be reported to the FDA in addition to the IRB and OHRP

Contact Information

Steven Hirschfeld, MD PhD

Associate Director for Clinical Research

National Institute of Child Health and Human
Development

31 Center Drive, Room 2A03

Bethesda, MD 20892-2425

Telephone: 301 496 0044

Facsimile: 301 496 1104

E-mail: hirschfs@mail.nih.gov