7/7/08

Reportable Events Session

Dr. Darcy Spicer

1. FDA: Adverse Events (Amdur, Chapter 7-3)
    a. Not found in Regs, found in FDA Information Sheets
    b. Explain criteria: Unanticipated, related or possibly related, serious
    c. Internal versus external (auto-acknowledged/HSIRB review)
    d. Describe multicenter trials and adverse event process
    e. AE Reporting to FDA: PI to FDA and/or Sponsor

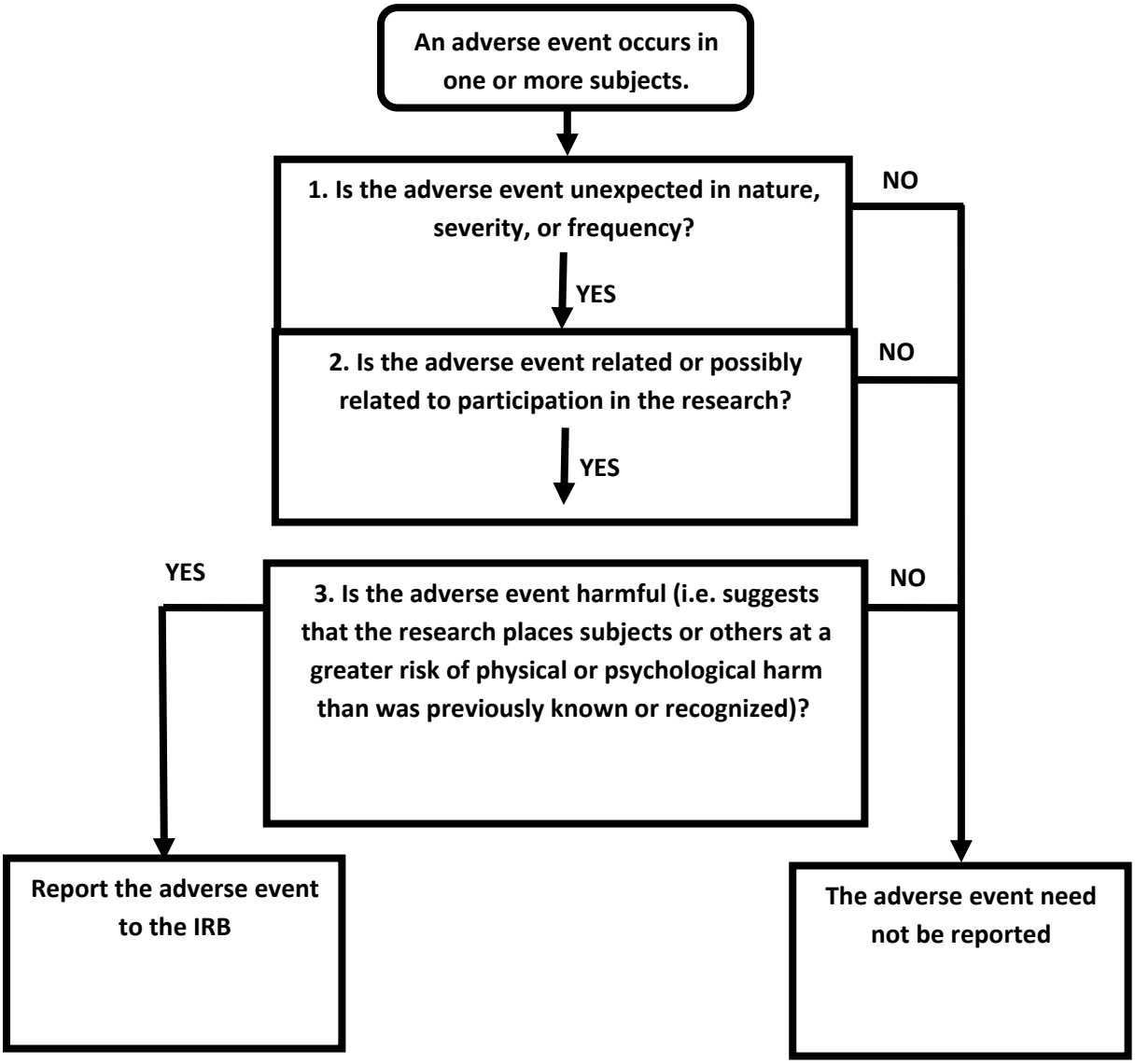
2. HHS: Unanticipated Problems Involving Risks to Others (UPX)
    a. UPX comes from The Common Rule
    b. Explain criteria: unexpected, related or possibly related, harmful
    c. When IRB review required
    d. Reporting to OHRP: PI to IRB, IRB to OHRP

3. Overlap of SAE's and UPX
    a. Overlap = rare occurrence
    b. Examples of SAE/UPX overlap

4. Data and Safety Monitoring (Amdur, Chapter 5-9 and 7-4)
    a. DSM, 1 of the 7 criteria for IRB approval (HHS and FDA regs)
    b. What is a DSMB, what does a DSMB do
    c. Raise question of researcher safety, others safety
    d. Discuss IRB evaluation of DSM plan

5. Non-Compliance, Complaints, Deviations, Terminations/Suspensions (Amdur 7-5)
    a. Definitions and examples of: Noncompliance, Serious Noncompliance, Continuing Noncompliance
    b. Definitions and examples of : Suspension, Termination
    c. What is a Protocol Deviation? How and to who are they reported?
    d. IRB reporting requirements of UPX, Noncompliance, Terminations/Suspensions
    e. How are complaints from subject or others handled

Determination of External Adverse Event Required Reporting



Definitions

External adverse events (EAEs):	Adverse events (AEs) experienced by subjects enrolled in multicenter clinical trials at sites other than the site(s) over which the USC IRB has jurisdiction.
Internal adverse events:	AEs experienced by subjects enrolled at the site(s) under USC IRB's jurisdiction.
Reasonably related:	An event is defined as reasonably related to the research if it is more likely to be caused by the research procedures than not.
Harmful Adverse Event	The adverse event suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.
Serious Adverse Event (SAE):	An event is defined as being serious if the event adversely alters the relationship between risks and benefits and includes events that either result in or require intervention to prevent, for example: 1) Inpatient hospitalization or prolongation of hospitalization; 2) Life-threatening reactions; 3) Persistent or significant disability/incapacity or permanent harm or disability (either physical or psychological); 4) Jeopardizing the subject; 5) A congenital anomaly/birth defect in the offspring of the subject; 6) A breach of confidentiality that may have a negative consequence; 7) Death.
Unanticipated problems involving risks to subjects or others (UPX):	Any event that is unexpected, related or possibly related, and harmful (i.e. suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized).

Suspension of IRB Approval:	When the IRB temporarily or permanently withdraws approval of some or all research activities. Suspended research is still under the jurisdiction of the IRB.
Termination of IRB Approval:	When the IRB permanently withdraws approval of ALL research activities. Terminated research is no longer required to undergo continuing review.

Noncompliance:	Failure to follow the regulations governing human research or failure to follow the requirements or determinations of the IRB. This definition may include action of any University employee or agent, such as investigators, research staff, IRB member, IRB staff, employees or institutional officials.
Serious Noncompliance:	An action or omission by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject.
Continuing Noncompliance:	A pattern of repeated actions or omissions by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that indicates a pattern of deficiency in the ability or willingness of an individual to comply with federal regulations, USC HSPP policy, or determinations or requirements of the USC HSPP.

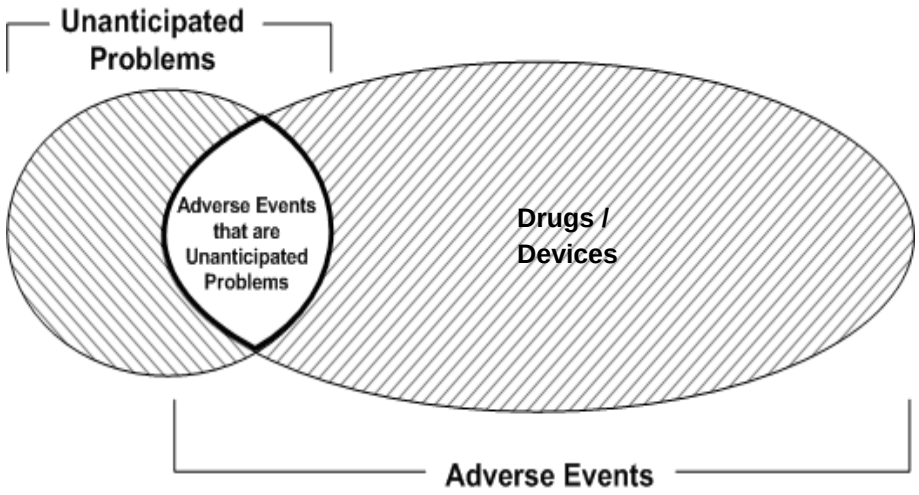
Reporting of Unanticipated Problems or Adverse Events to the IRB

	Unanticipated Problems Involving Risks to Subjects or Others	Adverse Events (Internal/External)
Regulations	**HHS**: Protection of Human Subjects (45 CFR 46)	**FDA**: Investigational New Drug Applications (21 CFR 312.32) Investigational New Device Exemptions (21 CFR 812.150)
Context	occurs in clinical or non-clinical research	occurs in clinical research only
Scope	untoward event in **ANY** aspect of a research study	untoward response to a **test article** (e.g. drug, device, biologic)
Involve	anyone (i.e. research staff, subjects, or others not directly involved in the research)	subjects only
Expectation	unanticipated	anticipated or unanticipated
Reporting	prompt reporting to IRB required (not to exceed 10 working days)	prompt reporting to IRB required when applicable (not to exceed 10 working days)
How to Report	iStar reportable event application	iStar reportable event application

Unanticipated Problems and/or Adverse Events: Overlap

Most adverse events are not unanticipated problems and vice-versa, although they may overlap.

(found in HHS regs only, 45 Part 46)



(found in FDA regs only, 21 CFR 312.32 & 21 CFR 812.150)

IRB Reporting of Unanticipated Problems Involving Risks to Subjects or Others (UPX) and Serious Adverse Events (SAE)

Unanticipated Problems involving Risks to Subject or Others (UPX)	Unanticipated Problems / Adverse Event (Overlap)	Serious Adverse Event* (SAE)
when applicable IRB reports to:	***when applicable IRB reports to:***	***when applicable IRB reports to:***
OHRP (if federally funded)	OHRP (if federally funded)	FDA (if subject to FDA regulations)
Funding agency (if federal agency)	FDA (if subject to FDA regulations)	Sponsor
Institutional Official (all are reported)	Sponsor	Funding Agency (if federal agency)
Principal Investigator	Funding agency (if federal agency)	Institutional Official (all are reported)
Department Chair / Director / PI's supervisor	Institutional Official (all are reported)	Principal Investigator
All IRB Chairs	Principal Investigator	Department Chair / Director / PI's supervisor
Grants and Contract Services	Department Chair / Director / PI's supervisor	All IRB Chairs
Other institutional committees (e.g., IBC)	All IRB Chairs	Grants and Contract Services
OPRS	Grants and Contract Services	Other institutional committees (e.g., IBC)
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	OPRS	

FDA: Adverse Events

- Not found in Regs, found in FDA Information Sheets
- Explain criteria: Unanticipated, related or possibly related, serious
- Internal versus external (auto-acknowledged/HSIRB review)
- Describe multicenter trials and adverse event process
- AE Reporting to FDA: PI to FDA and/or Sponsor

FDA Regulatory Issues

- All clinical studies must be reviewed an approved by an IRB consistent with the requirements of 21 CFR 50 (Protection of Human Subjects) and 56 (Institutional Review Boards), and either part 312 (Investigational New Drug Application) or part 812 (Investigational Device Exemptions).
- 56.108(a)(3),(4),(b) IRBS must have information concerning unanticipated problems and changes in the research activity.

IND Regulatory Issues for Investigators and Sponsors

- Investigators are required to report promptly to the sponsor any adverse event that may be reasonably be regarded as caused by or probably caused by the drug.
- Investigators are required to report promptly to the IRB all unanticipated problems involving risks to subjects or others (56.108(b)91), 312.53(c)(1)(vii).

- Sponsors are required to keep each participating investigator informed of new observations discovered by or reported to the sponsor particularly with respect to adverse effects and safe use.
- Sponsors are required to notify all participating investigators of any adverse experience associated with the use of the drug that is both serious and unexpected and any finding from tests in laboratory animals that suggests a significant risk for human subjects.

- Sponsors are required to identify in these IND safety reports all previous safety reports concerning similar adverse experiences and to analyze the significance of the current adverse experience in light of the previous reports.

IDE Regulatory Issues for Investigators and Sponsors

- Investigators are required to submit to the reviewing IRB and the sponsor a report of any unanticipated adverse device effect (UADE) occurring during an investigation.
- Sponsors must immediately conduct and evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs and participating investigators.

Adverse Events

- 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 (modified from the definition of adverse events in the 1996 International Conference on Harmonization E-6 Guidelines for Good Clinical Practice).

- ***External adverse event:*** From the perspective of one particular institution engaged in a multicenter clinical trial, *external adverse events are those adverse events experienced by* subjects enrolled by investigators at other institutions engaged in the clinical trial.
- ***Internal adverse event:*** From the perspective of one particular institution engaged in a multicenter clinical trial, *internal adverse events are those adverse events experienced by* subjects enrolled by the investigator(s) at that institution. In the context of a single-center clinical trial, all adverse events would be considered *internal adverse events.*

- ***Possibly related to the research:*** There is a reasonable possibility that the adverse event, incident, experience or outcome may have been caused by the procedures involved in the research (modified from the definition of *associated with use of the drug in FDA regulations at* 21 CFR 312.32(a)).

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

(1) 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

(2) 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.

Serious adverse event: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

(1) results in death;

(2) is life-threatening (places the subject at immediate risk of death from the event as it occurred);

(3) requires inpatient hospitalization or prolongation of existing hospitalization;

(4) results in a persistent or significant disability/incapacity;

(5) results in a congenital anomaly/birth defect; or

(6) 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 (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).

Reporting Internal Adverse Events to the IRB

- Upon becoming aware of an internal adverse event, the investigator should assess whether the adverse event represents an unanticipated problem and if so the investigator must report it promptly to the IRB (45 CFR 46.103(b)(5)).
- The investigator also must ensure that the adverse event is reported to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, an independent medical monitor, or a DSMB/DMC) *if required under the monitoring provisions described in the IRB-approved protocol or by institutional policy.*

Policy Guidance for External Adverse Event Reporting

- Regulation 21 CFR 312.32(c) indicates that sponsors shall notify FDA and all participating investigators in a written IND safety report of any adverse experience associated with the use of the drug that is both serious and unexpected.

Reporting External Adverse Events to the IRB

When an investigator receives a report of an external adverse event, the investigator should review the report and assess whether it identifies the adverse event as being:

(1) unexpected;

(2) related or possibly related to participation in the research; and

(3) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.

Only external adverse events that are identified in the report as meeting all three criteria must be reported promptly by the investigator to the IRB as unanticipated problems under HHS regulations at 45 CFR 46.103(b)(5). Institutional policy determines whether others must be submitted for review.

HHS: Unanticipated Problems Involving Risks to Others

- UPX comes from The Common Rule
- Explain criteria: unexpected, related or possibly related, harmful
- When IRB review required
- Reporting to OHRP: PI to IRB, IRB to OHRP

Unanticipated Problems

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.

Impact of Unanticipated Problems

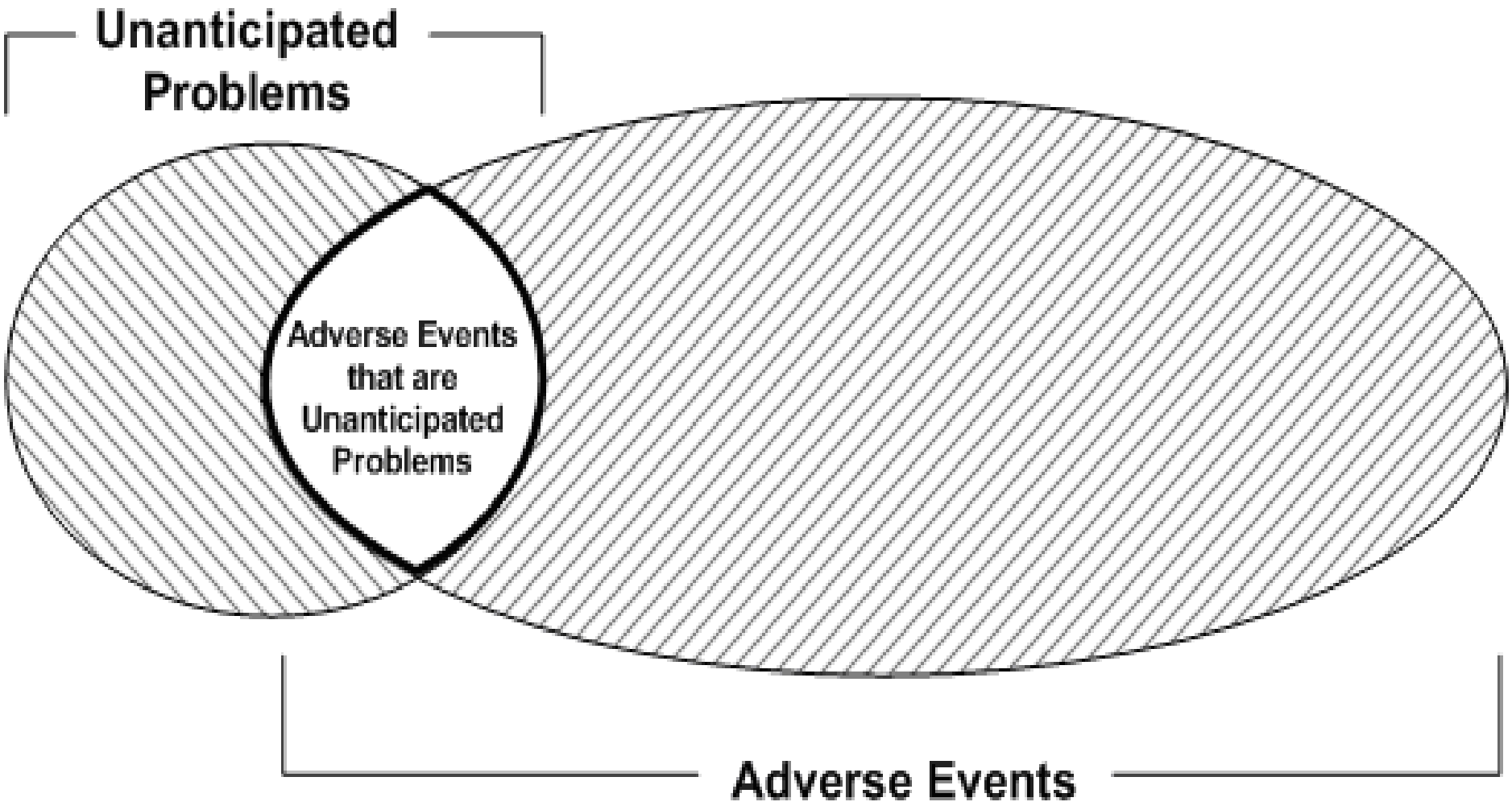
- Consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

Overlap of SAE's and UPX

- Overlap = rare occurrence
- Examples of SAE/UPX overlap

AEs and Unanticipated Problems

- Only a small subset of adverse events occurring in human subjects participating in research will meet the three criteria for an unanticipated problem.
- Furthermore, there are other types of incidents, experiences, and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk of harm, but no harm occurs.*


Unanticipated Problems
Adverse Events that are Unanticipated Problems
Adverse Events

Data and Safety Monitoring

- Monitoring, 1 of the 7 criteria for IRB approval (HHS and FDA regs)
- What is a DSMB, what does a DSMB do
- Raise question of researcher safety, others safety
- Discuss IRB evaluation of DSM plan

46.111 Criteria for IRB approval of research

(1) Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by §46.116.

(5) Informed consent will be appropriately documented, in accordance with, and to the extent required by §46.117.

(6) When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

GUIDELINES FOR NIH INTRAMURAL INVESTIGATORS AND INSTITUTIONAL REVIEW BOARDS ON DATA AND SAFETY MONITORING

- On June 5, 2000, NIH issued "Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials", which, together with an earlier policy for Phase III and IV trials, issued in June, 1998, requires Principal Investigators to submit a general description of a data and safety monitoring plan as part of their research protocols.

NIH: Elements involved in data and safety monitoring:

(a) The Principal Investigator (PI) must include a data and safety monitoring plan in each new protocol;

(b) The IRB must approve the plan and determine what kind of safety monitoring process (if any) is required: e.g., PI monitoring only; a single independent monitor, or a data and safety monitoring board (DSMB);

(c) The Institute Clinical Director is responsible for appointing an independent monitor or convening a DSMB (if an applicable Institute DSMB does not already exist - see 4, below);

(d) The PI is responsible for providing all required data to the individual monitor or the DSMB and for acting upon any findings made by the DSMB or monitor.

Type of Monitoring

- For many phase I and phase II trials, independent monitors or data and safety monitoring boards (DSMBs) may not be necessary or appropriate, particularly if the protocol involves no more than minimal risk. Continuous, close monitoring by the PI, with prompt reporting of serious adverse events to the IRB (and others, as appropriate) may be adequate.

Protocols that typically require a DSMB include:

- Protocols that generate blinded/randomized data
- Multicenter protocols presenting more than minimal risk to subjects
- Protocols using gene transfer or gene therapy methodology.

Protocols that may require a DSMB or an individual independen monitor include:

- Protocols that pose more than minimal risk to the subjects
- Protocols that the sponsor believes require special scrutiny because of high public interest or public perception of risk

When is a DSMB Needed (Amdur)?

- A large study population.
- Multiple study sites.
- Highly toxic therapies or dangerous procedures.
- High expected rates of morbidity or mortality in the study population.
- High chance of early termination.

Responsibilities and Functions of DSMBs (NIH)

Although the responsibilities and functions of DSMBs and independent monitors are not mandated by regulation, their role in protecting the safety of human subjects is critical, and includes:

- Examining safety and efficacy data and other records from protocols on an explicitly defined schedule
- Making findings and interpreting data including reporting information to the PI, IRB and IC Clinical Director about continuation, modification, suspension or termination of protocols based on observed beneficial or adverse effects of any of the experimental treatments under study
- Reviewing the general progress and conduct of the study.

Definition of DSMB (Amdur)

- Multidisciplinary group assuring the safety of participants and scientific integrity of the stud
- Three to 6 persons
- Experts in medical issues of the disease under study
- Experts in method issues
- Possibly ethics experts
- Monitor the timeliness of accrual, quality of data, accumulating outcomes

What does a DSMB do (Amdur)?

- Review data at predetermined intervals.
- Sometimes operate under protocol specified rules for study termination/continuation.
- May specify the type and form of data, examine blinded data by group or completely unblind.
- Decisions are suggestions to sponsors/investigators.

Study Termination

- Efficacy – study question answered.
- Futility – the study question will not be addressed.
- Safety – risks are too high.

- IRBs should review DSMB or independent monitor reports as they are received, and not wait to do so until the time of continuing review.

Non-Compliance, Complaints, Deviations, Terminations/Suspensions

- Definitions and examples of: Noncompliance, Serious Noncompliance, Continuing Noncompliance
- Definitions and examples of : Suspension, Termination
- What is a Protocol Deviation? How and to who are they reported?
- IRB reporting requirements of UPX, Noncompliance, Terminations/Suspensions
- How are complaints from subject or others handled

Noncompliance: Failure to follow the regulations governing human research or failure to follow the requirements or determinations of the IRB. This definition may include action of any University employee or agent, such as investigators, research staff, IRB member, IRB staff, employees or institutional officials.

Serious Noncompliance: An action or omission by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that any other reasonable individual would have foreseen as compromising the rights and welfare of a subject.

Continuing Noncompliance: A pattern of repeated actions or omissions by an individual (e.g., investigator, research staff, IRB member, IRB staff, employee or institutional official) that indicates a pattern of deficiency in the ability or willingness of an individual to comply with federal regulations, USC HSPP policy, or determinations or requirements of the USC HSPP.

45 CVF 46.103 (b)(5)

- Written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the Department or Agency head of (i) any unanticipated problems involving risks to subjects or others, as well as any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB, and (ii) any suspension or termination of IRB approval.

45 CFR 46.113 and 21 CFR 56.113

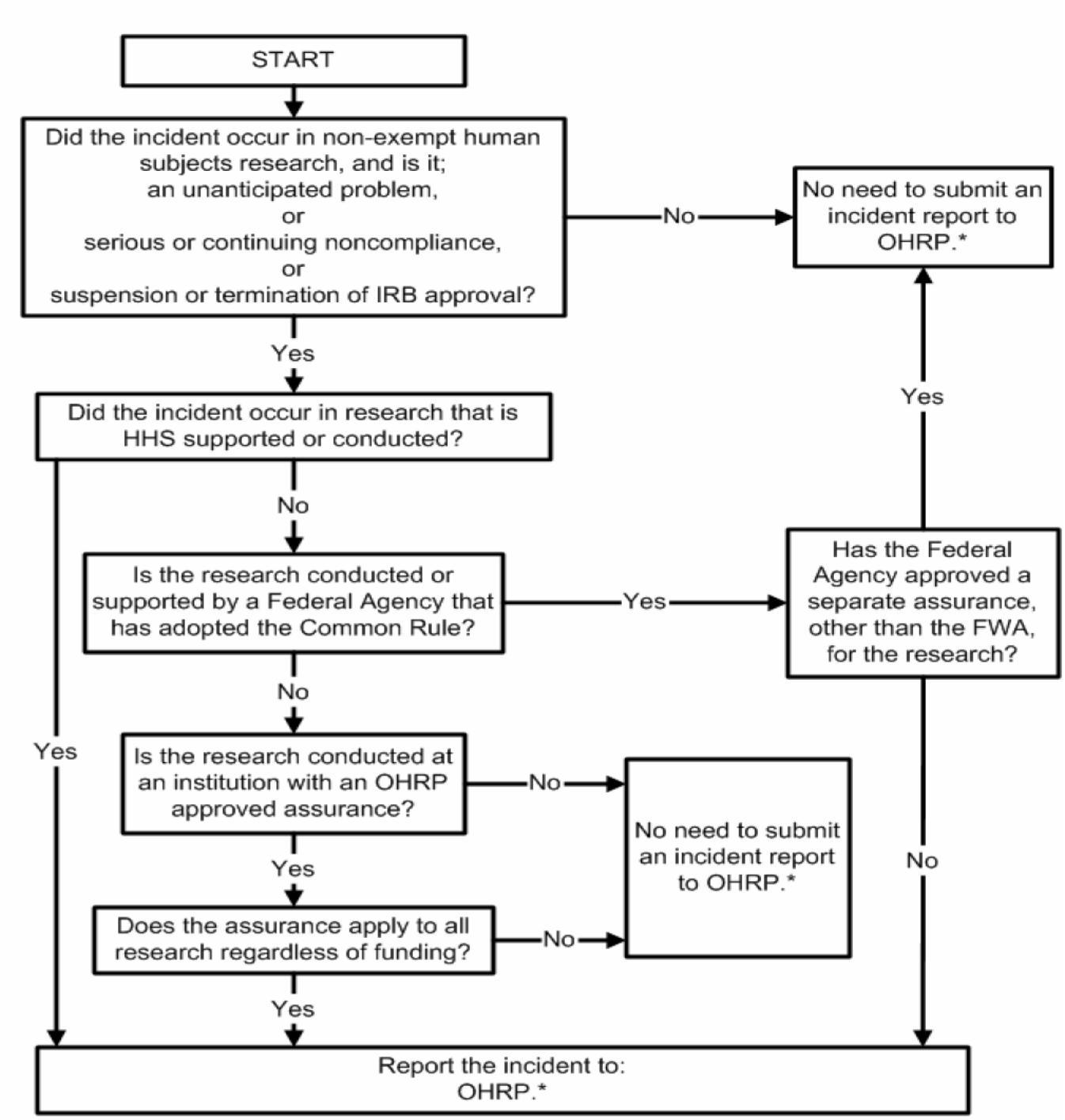
- Suspension or termination of IRB approval of research. An IRB shall have the authority to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action, and shall be reported promptly to the investigator, appropriate institutional officials and the Department or Agency head.

Suspension of IRB Approval: When the IRB temporarily or permanently withdraws approval of some or all research activities. Suspended research is still under the jurisdiction of the IRB.

Termination of IRB Approval: When the IRB permanently withdraws approval of ALL research activities. Terminated research is no longer required to undergo continuing review.

Reporting to OHRP

- In general, these reporting requirements apply to all nonexempt human subjects research that is:
- (a) conducted or supported by HHS;
- (b) conducted or supported by any non-HHS federal department or agency that has adopted the Common Rule and is covered by a Federal wide Assurance (FWA) determined to be appropriate for such research; or
- (c) covered by an FWA, regardless of funding source.


START
Did the incident occur in non-exempt human subjects research, and is it; an unanticipated problem, or serious or continuing noncompliance, or suspension or termination of IRB approval?
No
No need to submit an incident report to OHRP.*
Yes
Did the incident occur in research that is HHS supported or conducted?
Yes
No
Is the research conducted or supported by a Federal Agency that has adopted the Common Rule?
Yes
Has the Federal Agency approved a separate assurance, other than the FWA, for the research?
Yes
No
Yes
Is the research conducted at an institution with an OHRP approved assurance?
No
No need to submit an incident report to OHRP.*
Yes
Does the assurance apply to all research regardless of funding?
No
Yes
Report the incident to: OHRP.*

For unanticipated problems involving risks to subjects or others:

- Name of the institution (e.g., university, hospital, foundation, school, etc) conducting the research;
- Title of the research project and/or grant proposal in which the problem occurred;
- Name of the principal investigator on the protocol;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- A detailed description of the problem; and
- Actions the institution is taking or plans to take to address the problem (e.g., revise the protocol, suspend subject enrollment, terminate the research, revise the informed consent document, inform enrolled subjects, increase monitoring of subjects, etc.).

For serious or continuing noncompliance:

- Name of the institution (e.g., university, hospital, foundation, school, etc) conducting the research;
- Title of the research project and/or grant proposal in which the noncompliance occurred;
- Name of the principal investigator on the protocol;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- A detailed description of the noncompliance; and
- Actions the institution is taking or plans to take to address the noncompliance (e.g., educate the investigator, educate all research staff, suspend the protocol, suspend the investigator, conduct random audits of the investigator or all investigators, etc.).

For suspension or termination:

- Name of the institution (e.g., university, hospital, foundation, school, etc) conducting the research;
- Title of the research project and/or grant proposal in which the noncompliance occurred;
- Name of the principal investigator on the protocol;
- Number of the research project assigned by the IRB and the number of any applicable federal award(s) (grant, contract, or cooperative agreement);
- A detailed description of the reason for the suspension or termination; and
- The actions the institution is taking or plans to take to address the suspension or termination (e.g., investigate alleged noncompliance, educate the investigator, educate all research staff, require monitoring of the investigator or the research project, etc.)

Time frame for reporting incidents

- The regulations at 45 CFR 46.103(a) and (b)(5) do not specify a time frame for reporting, except Apromptly.@ For a more serious incident, this may mean reporting to OHRP within days. For a less serious incident, a few weeks may be sufficient. It may be appropriate to send an initial report, and indicate that a follow-up or final report will follow by the earlier of:
- a specific date; or
- when an investigation has been completed or a corrective action plan has been implemented.