

Unanticipated Problems and Adverse Events

David Borasky, MPH, CIP

Office of Research Protections

RTI International

Research Triangle Park, North Carolina, USA

Introduction

- IEC review of unanticipated problems and adverse events is plagued by confusion and inconsistency. This module is designed to offer guidance.
- Where regulation or guidance is lacking in clarity or is incomplete, definitions and recommendations are based on common or best IEC practice

Cause for Confusion

- US regulations use the term “unanticipated problem involving risk to the subject or others,” hereafter called a UP
- US drug regs use the term “adverse effect,” hereafter called an AE
- US device regs use the term “adverse device effect,” hereafter also called an AE

Cause for Confusion

- ICH: Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product .

Learning Objectives

- Define a UP and clarify its relationship to an AE
- Discuss IEC review of UPs
- Determine whether or not the scenario describes a UP

Objective 1:

*Unanticipated Problems Involving Risk
to the Subject or Others*

Question

What is the difference between a UP and an AE?

Unanticipated Problem (UP)

A UP is any event or outcome that meets the following three UP criteria:

- It is unexpected
- It is related or possibly related to the research
- The subject or other individual is placed at greater risk of harm than initially anticipated by the IEC

NOTE: An event or outcome refers to 1) an event involving risk to the subject or others (e.g., an AE, non-compliance, a protocol deviation) or 2) new information on risk which becomes available to the PI or IEC.

Criterion #1

The event or outcome was unexpected, in terms of specificity, frequency, or severity, given the nature of the research and the subject population.

NOTE: The terms “unanticipated” and “unexpected” are considered to be synonymous.

Criterion #2

There is a reasonable possibility based upon the available information that the event or outcome may have been caused by or resulted from participation in the research by the subject(s) (i.e., related or possibly related).

NOTE: Causality does not have to be absolutely established.

Criterion #3

Subjects or others are placed at a greater risk of harm or discomfort than was considered by the IEC when it approved the research, either initially or at continuing review.

NOTE: There may be only exposure to risk, or the risk may culminate in a subject or another individual experiencing a harm or discomfort (e.g., an AE). Harm or discomfort may be physical, psychological, social, legal, or economic. As discomfort intensifies, it can rise to the level of a harm.

Adverse Event (AE)

- An AE is any untoward or unfavorable medical occurrence in a human subject (a physical or psychological harm) temporally associated with the subject's participation in the research (whether or not related to participation in the research).
- AEs can be classified as internal i.e., those which occur at a study site(s) under the jurisdiction of the IEC of record.
- AEs can be classified as external i.e., those which occur at study sites (e.g., a multicenter clinical trial) under the jurisdiction of other (external) IECs.
- AEs commonly occur in clinical research as opposed to behavioral and social science research.
- AEs may be serious or not serious.

Serious Adverse Event (SAE)

Any AE that results in death, a life-threatening situation, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability, a birth defect, and other events that may not result in death, be life-threatening, or require hospitalization which require medical intervention to prevent one of the outcomes listed above.

Based on 21 CFR 312.32(a)

UP vs. AE

- Most AEs are not UPs
- AEs that are unrelated to the research or there is simply insufficient information to address causality are not UPs
- AEs that are expected in terms of specificity, severity, and frequency (e.g., described in the protocol, Investigator Brochure, the literature, or the consent form) are not UPs
- AEs that do not place subjects at greater risk of harm than was considered by the IEC when it approved the research are not UPs
- AEs that are serious are more likely to be a UP than AEs that are not serious

Examples

- Nausea and vomiting from chemotherapy is an AE
- Nausea and vomiting from chemotherapy is not a UP because it is expected
- Sudden death from chemotherapy is an AE and a UP

NOTE: In order for an AE to be classified as a UP, it must satisfy the four criteria.

Examples (cont.)

- Stigmatization from a breach of confidentiality may be a UP, but is not an AE.
- Revocation of parole from a breach of confidentiality may be a UP, but is not an AE.
- Severe psychological stress from completing a survey on risk-prone behaviors may be a UP and an AE.

NOTE: Events which occur in Behavioral and Social Science research must satisfy the four criteria to be classified as a UP. It is possible that an event could occur in non-medical research, which would result in an AE.

Objective 2:

*IEC Review of Unanticipated Problems
Involving Risk to the Subject or Others*

Basis for Review

- ICMR: SAE reports from the site as well as other sites are reviewed by EC and appropriate action taken when required.
- WHO TDR: IEC should review “serious and unexpected adverse events related to the conduct of the study or study product, and the response taken by investigators, sponsors, and regulatory agencies; any event or new information that may affect the benefit/risk ratio of the study”

Basis for Review

- ICH-GCP: The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.
- US: prompt reporting to the IRB ... of any unanticipated problems involving risks to subjects or others

Initial Determination of a UP

The PI is responsible for making the initial determination that the event or outcome may be a UP and, accordingly, should be promptly reported to the IEC.

NOTE: The UP may involve an internal AE, other internal event, an external AE, or outcome information on risk provided by a sponsor, DSMB, FDA or other source.

Time Frame for Reporting UPs to the IEC and Institutional Officials

The time frame for prompt reporting of UPs to the IEC and Institutional Officials depends on the seriousness of the UP.

- ❑ UPs which are serious AEs or other serious events should be reported to the IEC ASAP, but no later than one week.
- ❑ All other UPs should be reported to the IEC no later than two weeks.
- ❑ The IEC, upon completion of its review, would report the UP to appropriate institutional officials (e.g., the IO) in a timely manner.

NOTE: 45 CFR 46 and 21 CFR 56 do not define “prompt.”

Information Needed by the IEC

1. Detailed description of the UP
2. Prognosis or outcome (if known)
3. Assessment of causality/relatedness
4. Procedures to minimize risk (if necessary)
5. Revised protocol (if necessary)
6. Updated risk-benefit relationship
7. Revised consent form (if necessary)
8. Addendum consent form (if necessary)

NOTE: The IEC should require, as necessary, more detail from the PI, sponsor, or DSMB.

IEC Review of UPs

1. Determine if additional procedures are required to minimize risk.
2. Determine if the protocol requires revision.
3. Determine if the risk-benefit relationship of the research is still acceptable.
4. Determine if the consent form requires revision.
5. Determine if subjects must be informed of new information.
6. Determine if the study should be suspended or terminated.
7. Determine if the UP is associated with serious or continuing non-compliance.

Objective 3:

Scenarios

Scenario 1

A subject enrolled in a Phase II active-control study evaluating a new investigational drug for treatment of psoriasis develops severe acute liver failure judged to be related to the study drug. The investigator's brochure and the CF identify mild elevation of liver enzymes as a risk.

Determination

- This is a UP because it is 1) unexpected, 2) related to the study drug, 3) the subject was placed at greater risk of harm than was considered by the IEC when it approved the research and 4) changes are needed to protect human subjects.
- The IEC might decide on a number of corrective actions, including an amended CF, provision of new risk information to currently enrolled subjects, and increased monitoring for hepatic toxicity.

Scenario 2

A subject enrolled in a clinical trial received a dose of an IND drug that is 2x's higher than the IEC approved dose. While the dosing error increased the risk of toxicity, the subject experienced no detectable adverse effects during an appropriate period of careful observation.

Determination

- This is a UP because it is 1) unexpected, 2) related to participation in the research, 3) the subject was placed at greater risk of harm than was considered by the IEC when it approved the research and 4) corrective actions are needed to protect human subject.
- The IEC might decide on a number of corrective actions, including informing the subject of the dosing error, and requiring the PI to develop a corrective action plan to minimize the possibility of future dosing errors.

Scenario 3

An investigator conducting a clinical trial received a report from the DSMB indicating a higher than expected risk of stroke associated with study drug (x).

Determination

- This is a UP because 1) the DSMB outcome analysis of a series of AEs concluded that strokes are occurring in the clinical trial at an unexpectedly high rate, 2) the outcome is related or possibly related to the study drug, 3) subjects are placed at greater risk of harm than was considered by the IEC when it approved the research, and 4) changes are needed to protect subjects.
- The IEC might decide on a number of corrective actions, including an amended CF, provision of new risk information to currently enrolled subjects, increased monitoring of subjects, and obtainment of future DSMB interim analysis reports.

Scenario 4

During a behavioral study, individually identifiable sensitive information about the sexual activity of subjects was stored on a laptop computer. The laptop computer was stolen from the investigator's car, creating a risk of breach of confidentiality.

Determination

- This is a UP because 1) it is unexpected, 2) related to participation in the research, and 3) the subject was placed at greater risk of harm than was considered by the IEC when it approved the research.
- The IEC might decide on a number of corrective actions, including informing the subject of the UP, and prohibiting the removal of research data from the facility either on a laptop or hard copy without encryption.

Scenario 5

An investigational biologic administered to the first two subjects in a Phase II clinical trial was not appropriately screened for viral contaminants, including HIV and Hepatitis B. The sexual partners of the subjects, in addition to the subjects, are at risk.

Determination

- This is a UP because 1) it is unexpected, 2) related to participation in the research, and 3) both the subject and others were placed at greater risk of harm that was considered by the IEC when it approved the research.
- The IEC might decide on a number of corrective actions, including informing the subjects of the UP, asking the subjects to inform their partners, and implementation of appropriate monitoring of both the subjects and their partners.

Scenario 6

A subject with advanced pancreatic cancer enrolled in a pain management study using hypnosis. During the first hypnosis session, the subject suffers cardiac arrest and dies. Autopsy revealed a massive pulmonary embolism.

Determination

- While this is an AE, it is not a UP because it is not related to the research.
 - The cardiac arrest was the result of the pulmonary embolism, which was not due to the research intervention, but due to the subject's underlying disease.
- It is therefore not necessary for the IEC to take any corrective action.

Scenario 7

A subject undergoing chemotherapy for leukemia has severe mucositis, which requires hospitalization for pain control and hydration, and subsequent dose adjustment. The risk of severe mucositis is clearly described in the protocol, the investigator's brochure and the consent form.

Determination

- While this is an AE, it is not a UP because it is expected.
- It is not necessary for the IEC to take any corrective action.

Scenario 8

During a psychology study evaluating reaction times in response to auditory stimuli, subjects are placed in a small, soundproof booth. One subject experienced claustrophobia and asked to withdraw from the research. The consent form disclosed the risk of claustrophobia.

Determination

- This is not a UP because the risk of claustrophobia was disclosed in the CF.
- It is not necessary for the IEC to take any corrective action at this time.

Reminder

- IECs should have clear standard procedures for reporting UPs and AEs.
- All UPs must be reported at the local and federal level in accordance with 45 CFR 46.
- AEs which may or may not be UPs must also be reported in accordance with the relevant guidelines and regulations.

References

1. United States Department of Health and Human Services. Office of Human Research Protections (OHRP). Guidance on Reviewing and Reporting Unanticipated Problems Involving Risk to the Subjects or Others and Adverse Events. Bethesda: US Dept. of Health and Human Services. January 15, 2007.
2. Kratochvil, CJ, Prentice, ED, Epperson, KJ, Gordon, BG. "Review of Adverse Events in Institutional Review Board." Institutional Review Board Management and Function Second Edition. Eds. Bankert, EA and Amdur, RJ. Sudbury: Jones & Bartlett Publishers, 2006. 257-261.