Adverse Event Module Part 4: Event Reporting to the IRB

Agenda

• Unanticipated problem (UP) reporting to the IRB
  • Adverse events
  • Non-adverse events
  • Corrective and Preventative Action (CAPA) Plans

What is an Unanticipated Problem (UP)

• AE or non-AE that meets all of the following criteria:
  • Unexpected (in terms of nature, severity, or frequency) given the research described in the IRB-approved protocol and informed consent document(s), or the IB; and the characteristics of the subject population being studied
  • Related or possibly related to participation in the research
  • Suggests the research may place the subject or others at a greater risk of harm (physical, psychological, economic, or social harm) than previously recognized
UP Algorithm

1. An incident, experience, or outcome
   - Is incident, experience, or outcome unexpected in nature, severity, or frequency?
     - NO
     - Is incident, experience, or outcome related or possibly related to participation in the research?
       - NO
       - Does the incident, experience, or outcome subject the research participant, subject or others at a greater risk of physical or psychological harm than was previously known or recognized?
         - NO
         - YES
   - NO
   - YES

The incident, experience, or outcome is an unanticipated problem.

The incident, experience, or outcome is not an unanticipated problem.

From: Office for Human Research Protections, 2007

HHS Regulations & Guidance

- 45 CFR Part 46.103(b)(5)
- OHRP Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events (2007)

Relationship of Unanticipated Problems (UPS) & AEs

- Subset of AEs also meet the criteria for being an UP
- Some UPS are not AEs

From: Office for Human Research Protections, 2007
Multi-site Research and External AEs

- Individual adverse events should only be reported to investigators and IRBs at all institutions when a determination has been made that the events meet the criteria for an UP
- Investigator submits to IRB
  - Clear explanation of why the AE/series of AEs is a UP
  - Description of any proposed protocol changes or other corrective actions to be taken by the investigators

FDA Regulations & Guidance

- Part 56.108(b) (1)
- IND: 312.66, 312.53(c)(1)(vii)
- IDE: 812.150(a)(1), 812.150(b)(1), 812.46(b), and 812.3
- FDA Guidance for Clinical Investigators, Sponsors, and IRBs Adverse Event Reporting to IRBs — Improving Human Subject Protection (2009)

IND & IDE Reporting Requirements to IRB

- IND:
  - Investigator sends safety reports from sponsor only if an UP
- IDE:
  - Investigator UADE no event later than 10 working days
  - Sponsors immediately conduct evaluation of UADE report to all reviewing IRBs within 10 working days
Non-AE UPs

- Incidents & outcomes
  - Research participants
  - Others
- Protocol deviation
- Non-compliance
  - Serious
  - Continuing
- Know IRB Policy

Routine Reporting to IRB

- Occurs at the time of continuing review
  - IRB must determine that all foreseeable risks have been identified and that the study still has a favorable risk benefit ratio
- Includes AEs and UPs that have occurred since the previous continuing review:
  - All AEs and UPs or
  - Statement that AEs that occurred were not at greater frequency or severity than what was previously known and no UPs
- Know how your IRB(s) wants to have this information summarized
Expedited Reporting: Incident Report

• Unanticipated problems
• Noncompliance with human subjects regulations or determinations of the IRB
• Applies to all human subjects research:
  • Conducted or supported by HHS
  • Conducted or supported by any non-HHS federal department or agency that has adopted the Common Rule and is covered by a Federalwide Assurance (FWA)
  • Covered by an FWA, regardless of funding source.

Investigator Reporting Timeframe

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<tr>
<th>Type of Unanticipated Problem</th>
<th>Reporting Timeline to IRB</th>
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<tr>
<td>Serious UPs</td>
<td>As soon as possible but no later than <strong>seven (7) days</strong> after Investigator awareness</td>
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<tr>
<td>Non-serious UPs</td>
<td>As soon as possible but no later than <strong>fourteen (14) days</strong> after Investigator awareness.</td>
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Incident Report

• Protocol identifiers
• Detailed description of the adverse event, incident, experience, or outcome
• Explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an UP
• Description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem
• IRB specific form or database
Corrective and Preventative Action (CAPA) Plan

- Ensures there is quality at every step during the study conduct
- Establish processes to identify, correct, and prevent future occurrences that may impact safety and data

CAPA Terminology

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<th>Terminology</th>
<th>Description</th>
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<tr>
<td>Corrective Action</td>
<td>Action to eliminate the cause of an occurrence (i.e., issue, problem, or undesirable situation).</td>
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<tr>
<td>Preventive Action</td>
<td>Action to eliminate the cause of a potential occurrence (i.e., issue, problem, or undesirable situation).</td>
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<tr>
<td>Root Cause Analysis</td>
<td>A problem solving method used to identify the origin of the cause(s) of occurrences (i.e., issues, problems or undesirable situation)</td>
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Preventive action is taken to prevent occurrence whereas corrective action is taken to prevent recurrence.

Crafting Your CAPA

Assess Cause/Root Cause Analysis
- Why did the event occurred? Is it a system problem? Problem with procedure? A training issue?

Plan for corrections and prevention
- Address ways to correct the event and prevent it from happening again

Document
- Specific corrective actions
- Preventive measures
- Number of subjects were affected in the current study; and did the problem extend to other studies that used the same processes
- Inadequate documentation of the corrective actions taken.
- Specify timeframe and who will be responsible for the components of the CAPA Plan.

Evaluate
- Audit/GA/QC
Corrective and Preventive Actions…

• Protocol:
  • Modify inclusion or exclusion criteria to mitigate the newly identified risks
  • Implement additional procedures for individual participant safety monitoring
• Informed consent
  • Modify to include new information about newly recognized risks to previously enrolled subjects
  • Inform enrolled subjects

…Corrective and Preventive Actions

• Suspend enrollment of new subjects
• Suspension of research procedures in currently enrolled subjects
• Increase monitoring activities
• Provide training/re-training
• Work with appropriate institutional officials to correct problem

Summary

• UPs are serious or pose a new risk
• Non-compliance compromises the protection of human subjects
• IRBs must review these expediously to see if the risk benefit ratio is still favorable