Adverse Events Part 4: Event Reporting to the IRB

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Outline

- Unanticipated Problem (UP)
- Corrective and Preventive Action (CAPA) Plans
- Additional IRB reporting

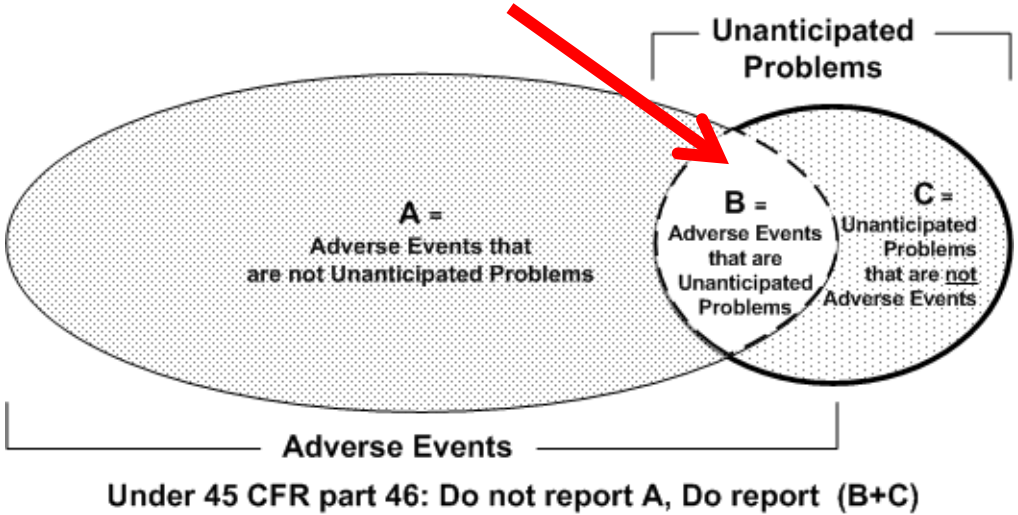
What is an Unanticipated Problem (UP)

- 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

45 CFR Part 46.108(a)(4)(i), 2018; OHRP Guidance Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007

Relationship of UPs & AEs

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



Under 45 CFR part 46: Do not report A, Do report (B+C)

OHRP Guidance Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events, 2007

FDA Regulations, Guidance & UPs

- Regulations
  - Part 56.108(b)(1)
  - IND: 312.53(c)(1)(vii), 312.66
  - IDE: 812.46(b), 812.150(a)(1), 812.150(b)(1)
- *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 per the IRB requirements
- IDE:
  - Investigator UADE no later than 10 working days
  - Sponsors immediately conduct evaluation of UADE report to all reviewing IRBs within 10 working

Investigator Reporting Timeframe

Type of Unanticipated Problem	Reporting Timeline to IRB
Serious UPs	As soon as possible but no later than **one (1) week** after Investigator awareness
Non-serious UPs	As soon as possible but no later than **two (2) weeks** after Investigator awareness.

Contents of the Report to IRB

- Identifying information for the research protocol,
- Detailed description of the adverse event, incident, experience, or outcome
- Explanation of the basis for determining that the AE, incident, experience, or outcome is a UP
- Description of any changes to the protocol or other corrective actions that have been taken or are proposed

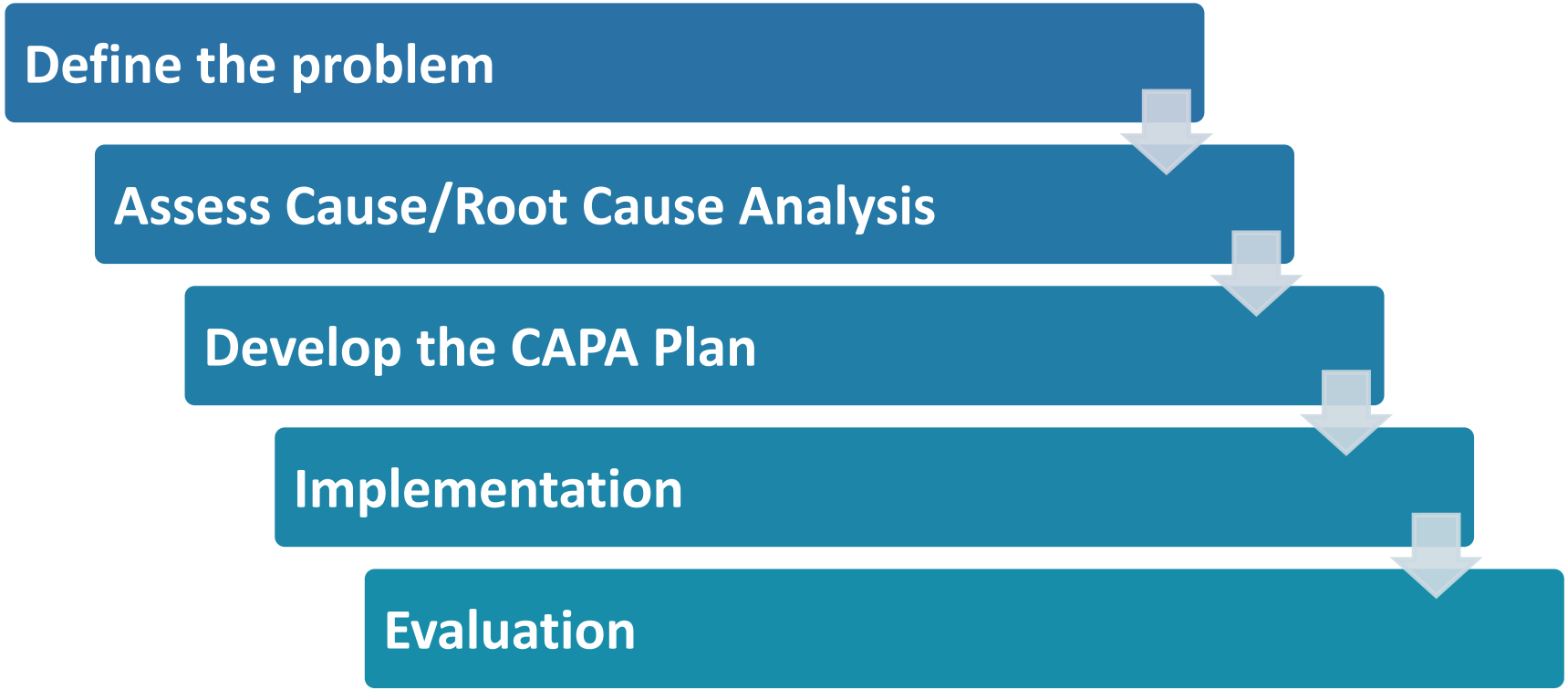
Corrective and Preventive Action (CAPA) Plan

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

CAPA Terminology

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

Crafting Your CAPA Plan



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

Other Reportable Information

- Non-compliance
- Major protocol deviation
- New information that might affect a participant's willingness to enroll or remain in the study
- Complaint
- Death of a subject at least possibly due to the research
- Audit findings
- Breach of confidentiality
- Change to the protocol taken without prior IRB review
- Incarceration of a subject
- Premature suspension or termination of the research

IRB Activities

- Review the UP or other information that is submitted
- May ask for more information
- Make a final determination
- If serious or continuing non-compliance or a UP, report to OHRP and if applicable, FDA

Summary

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

Test Your Knowledge

The study coordinator identified an adverse event that they believe is unexpected, not related to the research and not serious. The coordinator should report it to the IRB right away.

A. True
B. False

Test Your Knowledge

What is the process for developing a CAPA plan?

A. Describe the problem, describe the desired situation, list steps to move from problem to solution, assign a responsible party and due date to each step.
B. Describe the problem, explain who is responsible for the problem and why.
C. Describe the problem, describe the desired situation, report back on progress.
D. Describe the problem, describe the desired situation, list steps to move from problem to solution, determine exactly who caused the problem.