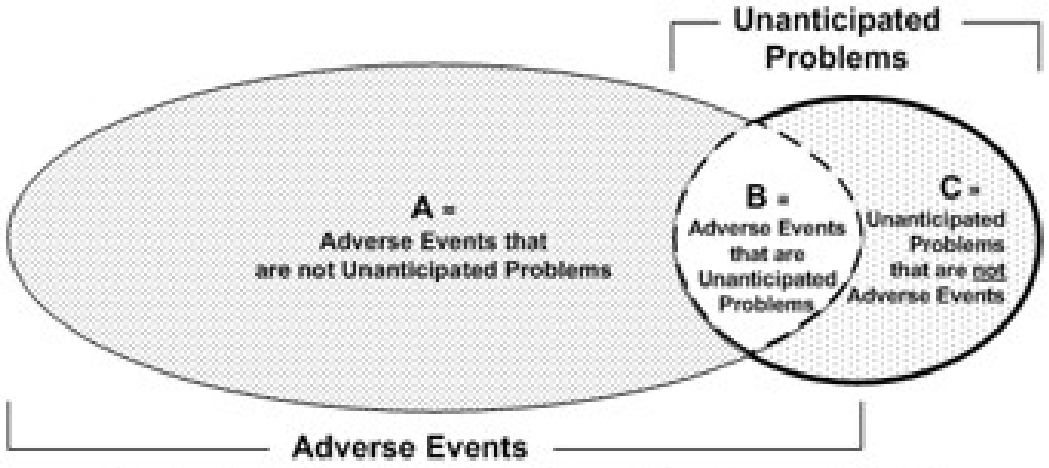
Unanticipated Problems One Criteria at a Time – *Increased Risk*

April 2025

Agenda

- Refresher
- Assessing whether an IEO indicates that the study presents an increased risk to subjects or others than previously known or recognized
  - OHRP
  - FDA
- References

Defining Unanticipated Problems



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

- Other names: UP, UPR, UPIRTSO, UPIRSO…
- Non-compliance or another **incident, outcome, or experience** can be an unanticipated problem
- Often will be a SAE, but not always
- Rule of thumb: if reviewing a reported SAE, you should consider whether it is a UPR or not

Defining Unanticipated Problems (in brief)

- A UPR is an incident, experience, or outcome (IEO) that is ***all three of the following:***
  - Unexpected
  - Related
  - Indicates that the study presents increased risks to subjects or others than previously known or recognized
- If the event does not meet one or more of these criteria, it is not a UPR
  - Only takes a “no” to any one of the three criteria to “kick it out” of being a UPR

Assessing Whether the IEO Represents Increased Risk - AEs

- If multi-center study, was it an ***internal*** event – did it happen at our local site?
  - If yes, investigator and IRB to assess
  - ***External*** events should be reviewed by monitoring entity (e.g., sponsor) for evaluation in context of other study data and reported to all sites promptly if the event is a UPR
- If the AE meets the first two criteria, and is a Serious AE, the AE would be a UPR
- Per OHRP, this is 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

Serious AE per OHRP

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

FDA – Implications & Significance

- Event would have implications for the conduct of the study
  - requiring a significant, and usually safety-related, change in the protocol such as revising inclusion/exclusion criteria or including a new monitoring requirement, informed consent, or investigator's brochure.
- Rate or severity of known/expected AE is greater than was previously thought
  - Rate - Subjects more likely to experience risk
  - Severity - Subjects exposed to possibility of a "worse" risk
- Specificity of event is not what IB described
- Devices: Unanticipated Adverse Device Effect (UADE) is a UPR
  - "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects"

What about IEOs that aren't AEs?

- Social or economic harm instead of the physical or psychological harm associated with adverse events
- Place subjects or others at increased *risk* of harm, but no harm occurs.
- Data losses/breach of confidentiality
- Error that exposes the involved subject to greater risk than the study was thought to present
- Audit reports that reveal compliance issues negatively impacting subject safety or rights

References

- Regulations:
  - FDA: 21 CFR 56.108(b)(1), 312.53(c)(1)(vii), and 312.66; 21 CFR 812.3(s)
  - OHRP: 45 CFR 46.103(b)(5)
- FDA Guidance: https://www.fda.gov/media/72267/download
- OHRP Guidance: https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html
- IRB Handbook Appendix A