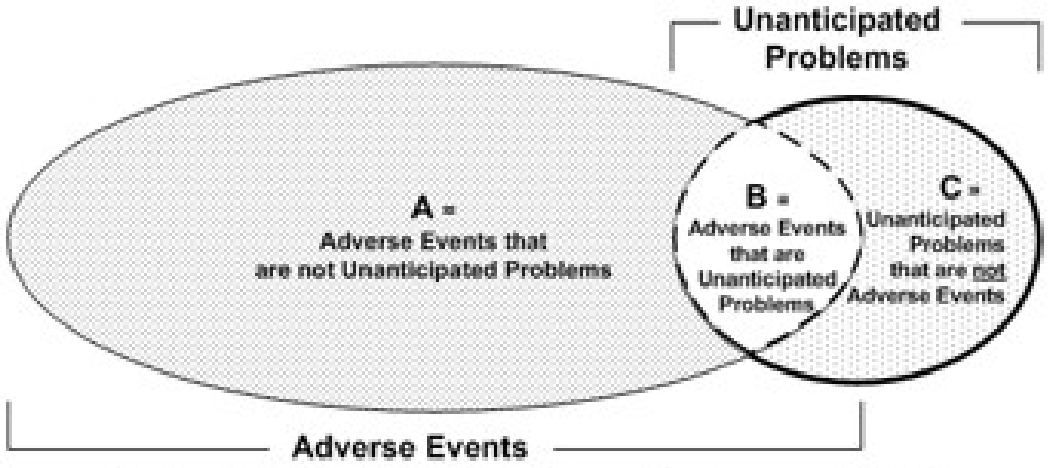
Unanticipated Problems One Criteria at a Time – *Relatedness*

April 2025

Agenda

- Refresher
- Assessing Relatedness
- 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
- First two criteria are usually easier to assess because we have resources to consult
- Third criteria is a judgment call and can be trickier to assess

Assessing Relatedness

- Relatedness often falls on a continuum:

Definitely related  Definitely Unrelated

- “Possibly related” means that there is a reasonable possibility that the adverse event may have been caused by the procedures involved in the research.
- Regulators realize that this can be a difficult assessment
- Our SOPs give a threshold for “reasonable possibility” as at least a 50% chance the IEO is causally related to the research procedures.

Assessing Relatedness

- An IEO may by cause by one or more of the following:
  1. The procedures involved in the research
  2. An underlying disease, disorder, or condition of the subject
  3. Other circumstances unrelated to study procedures or an underlying disease, disorder or condition of the subject
- If IEO is caused by #1 with at least 50% likelihood, the IEO is ***related to the research***
- Those caused by 2 or 3 would not be considered related to the research
- An IEO could have multiple causes

References

- Regulations:
  - FDA: 21 CFR 56.108(b)(1), 312.53(c)(1)(vii), and 312.66
  - 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