Unanticipated Problems One Criteria at a Time – *Expectedness*

March 2025

Agenda

- Regulations
- Background
- Defining
- Assessing Expectedness
- References

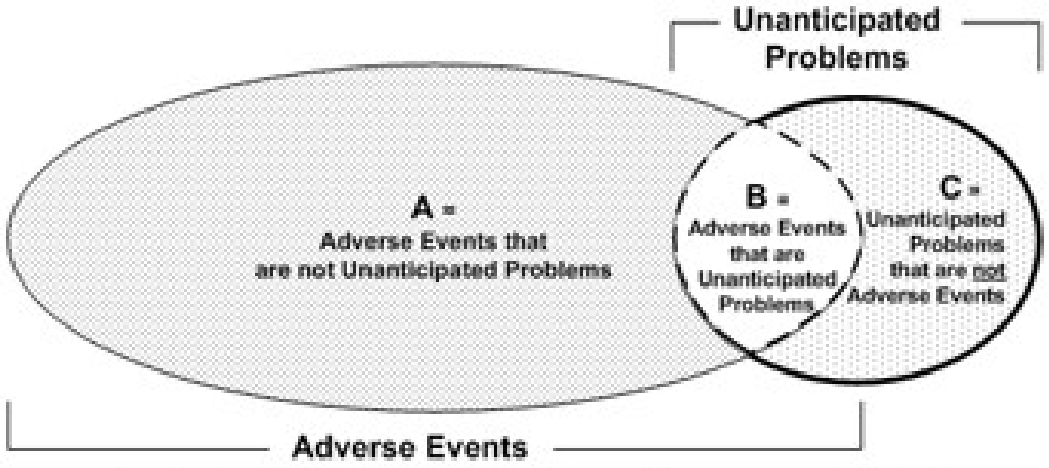
Regulations

- FDA
  - Investigators are to report promptly "to the IRB… all unanticipated problems involving risks to human subjects or others," (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).
  - https://www.fda.gov/media/72267/download
- OHRP
  - Institutions…must have written procedures for ensuring prompt reporting to the IRB…any unanticipated problem involving risks to subjects or others (45 CFR 46.103(b)(5)).
  - https://www.hhs.gov/ohrp/regulations-and-policy/guidance/reviewing-unanticipated-problems/index.html

Background

- "Unanticipated problem" not defined in regulations
- Prior state of affairs:
  - Sponsors and investigators submitting AEs to IRBs with no context or analysis
  - IRBs couldn't use the information meaningfully to assess risks to human subjects or to take steps to protect human subjects' rights & welfare
- 2007 OHRP Guidance & 2009 FDA Guidance issued to clarify what regulators see as an unanticipated problem
- Current state of affairs:
  - Sponsors monitor AE data for trends and alert investigators/IRBs (usually via investigators)
  - Investigators work with sponsor to analyze events occurring at their own sites (when related to data that the sponsor monitors, like AEs)
  - When there is no sponsor, or if investigator is sponsor/investigator, these responsibilities fall to the investigator

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 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 Expectedness

- Can refer to unexpected specificity, frequency, severity of an incident, experience, or outcome
- Consult the protocol-related documents:
  - IRB-approved research protocol,
  - Investigator brochure if relevant and there is one
  - Current IRB-approved informed consent document
  - Other relevant sources of information, such as product labeling and package inserts
- Consider the underlying condition of the subject, if any
  - Expected natural progression of any underlying disease, disorder, or condition of the subject(
  - Subject's predisposing risk factor profile for the adverse event

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