Monday Morning Practice Pearls #42

What is an unexpected adverse event (AE) and how to report to the IRB?

Below is a table comparing the definition of unexpected found in OHRP Guidance, FDA IND Safety Reporting 21 C.F.R. 312.32 and ICH GCP Guidelines. As you will see, they are all fairly similar.

United States Office of Human Research Protection (OHRP)	United States Food and Drug Administration (FDA)	International Conference on Harmonization (ICH)
Any adverse event occurring in one or more subjects participating in a research protocol, the nature, severity, or frequency of which is **not** consistent with either: 1. the known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; **or** 2. the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product)

When should an unexpected AE be reported to the IRB?

An unexpected AE should be reported to the IRB when it is an Unanticipated Problem (UP) using the PROTECT Reportable New Information (RNI) form.

A UP is defined as:

- Any incident, experience, or outcome that meets **ALL** of the following criteria:
  - **Unexpected** given the research procedures described in protocol related documents AND the characteristics of the subject population being studied
  - **Related or possibly related** to participation in the research
  - ***Suggests*** the research places the **subject or others at a greater risk** of harm than previously known or recognized

For more information on AEs and examples of reportable UPs, visit the AE learning module: https://ccrod.cancer.gov/confluence/display/CCRCRO/Adverse+Events.

KEY POINT

An AE can be unexpected and noted as such in C3D/Rave but may not be reportable to the IRB as a UP. If the unexpected AE is not a UP, it will be reported at the time of CR.