# Review of Adverse Events (AEs), Unanticipated Problems (UPs), and Noncompliance (NC)

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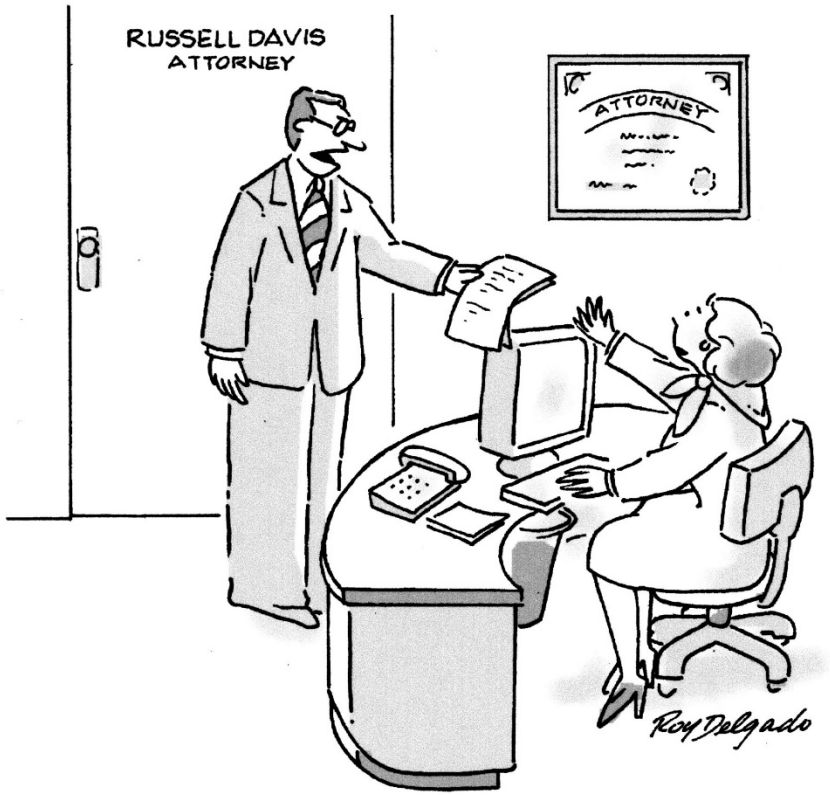
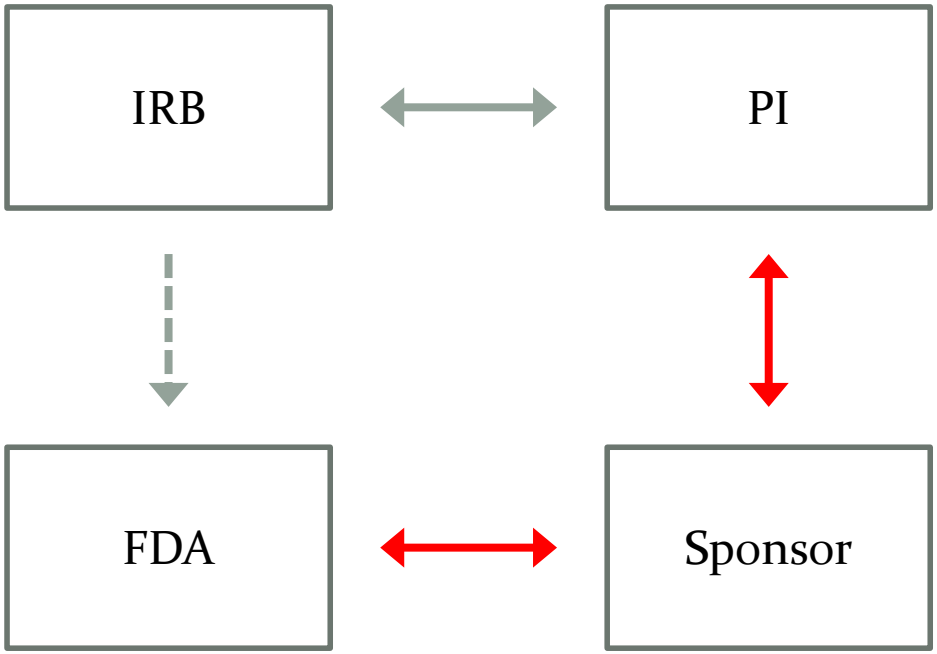
# AEs and UPs




*"Take this and make it much more difficult than it needs to be."*

- FDA and HHS have different definitions of adverse events (AEs) and unanticipated problems (UPs)
- FDA IND and IDE regulations have different definitions and requirements for reporting of adverse events

# Communication of AEs and UPs




"And this is good old Boston, the home of the bean and the cod,
Where the Lowells talk only to Cabots, and the Cabots talk only to God"
"Boston Toast" by John Collins Bossidy

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- Sponsors are required to report to PIs (and FDA) "any adverse experience associated with the use of the drug that is both serious and unexpected" (§ 312.32(c)(1)(i)(A))
- PIs are required to report to the IRB "all unanticipated problems involving risks to human subjects or others," including adverse events that should be considered unanticipated problems (§§ 56.108(b)(1), 312.53(c)(1)(vii), and 312.66).

- The IRB is required to report to the FDA "any unanticipated problems involving risks to human subjects or others." (§ 56.108(b))


"If you remember, I did mention possible side-effects."

# Adverse Events

## HHS
modified from 1996 ICH E-6 Guidelines

- any untoward or unfavorable medical occurrence
- temporally associated with the subject's participation in the research
- whether or not considered related to the subject's participation

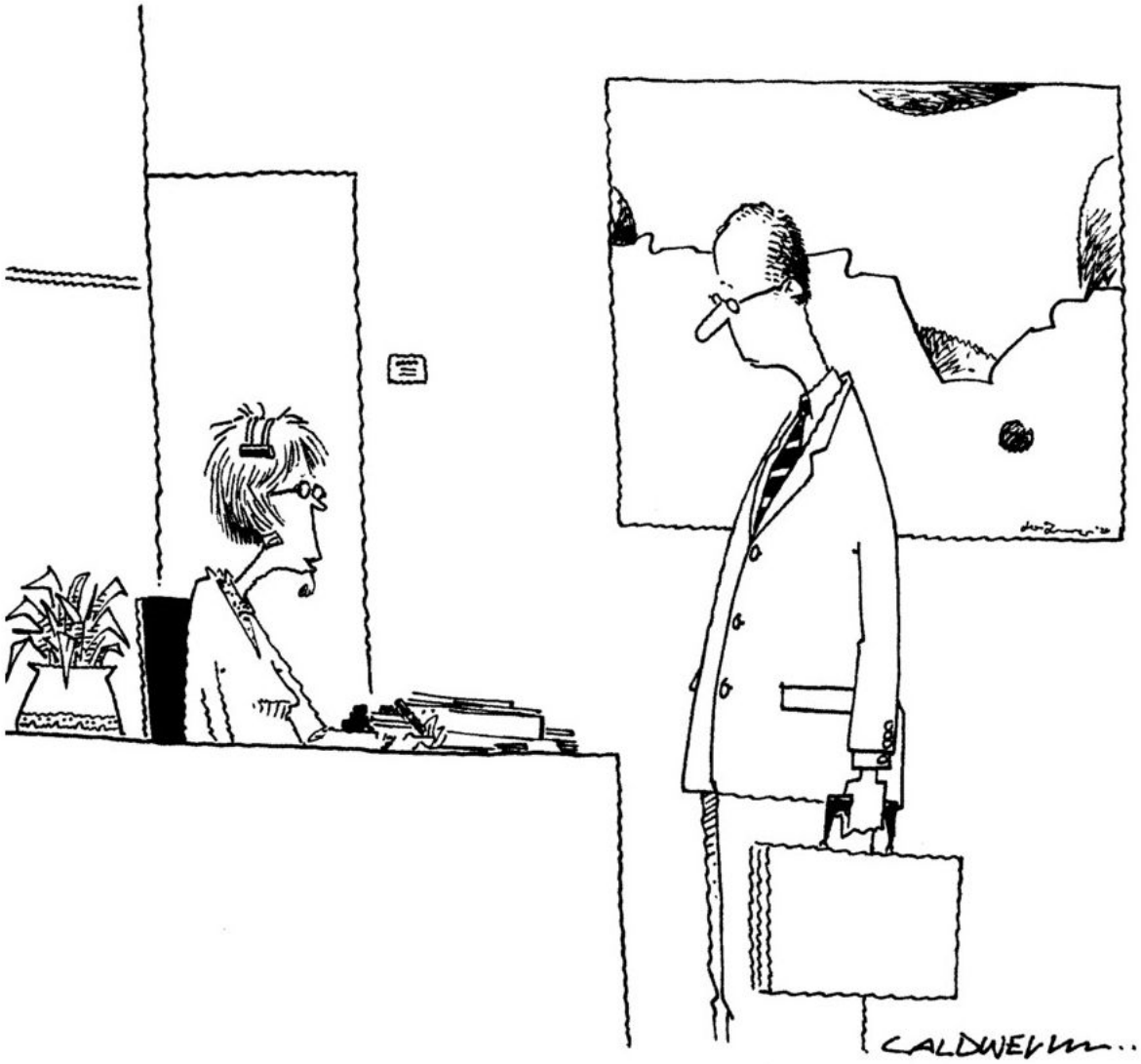
## FDA
21 CFR 312.32(a)

- any untoward medical occurrence
- associated with the use of a drug
- whether or not considered drug related

event associated with, but not necessarily related to …

# Serious Adverse Events

- An AE is considered serious if it results in any of the following outcomes (21 CFR 312.21(a)):
  - death
  - life-threatening adverse event
  - inpatient hospitalization or prolongation of existing hospitalization
  - a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
  - a congenital anomaly/birth defect, or
  - an important medical event that may require intervention to prevent one of the outcomes listed




"Is he expecting you? Or would you like to spring from behind a potted plant and yell 'surprise'?"

# Unanticipated Problems

## HHS

### OHRP Guidance (2007)

- An incident, experience, or outcome that is:
  - unexpected
  - related or possibly related
  - places subjects or others at a greater risk of harm than was previously known
- "generally will warrant consideration of substantive changes …"

# Unanticipated Problems

## HHS

OHRP Guidance (2007)

- An incident, experience, or outcome that is:
  - unexpected
  - related or possibly related
  - places subjects or others at a greater risk of harm than was previously known
- "generally will warrant consideration of substantive changes …"

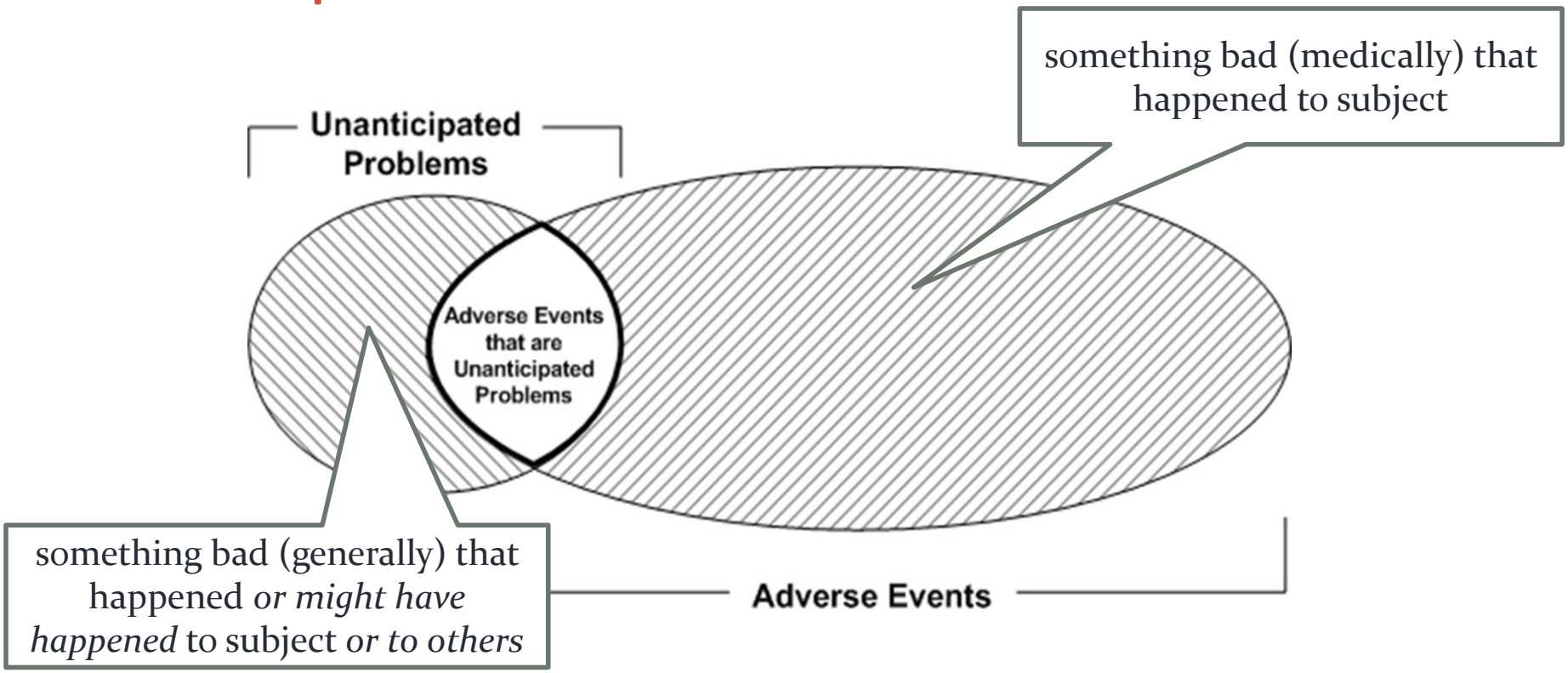
## FDA

FDA Guidance (2009)

- An untoward medical event that is:
  - unexpected
  - associated with the drug
  - serious
  - "would have implications for the conduct of the study …

an incident that is unexpected, related, serious (or places subjects or others at greater risk of harm) and warrants consideration of substantive changes (or has implications for the conduct of the study)

# Unanticipated Problems vs AEs




- IRB must report UPs to OHRP and/or FDA
- IRB does NOT need to report AEs

# Unanticipated Problem

- UNC definition (per OHRE SOP 6001)
- A UP is “any incident, experience, outcome, or new information that:
  - is unexpected (in terms of nature, severity, or frequency); AND
  - is at least possibly related to the research; AND
  - indicates that subjects or others are at a greater risk of harm … than was previously known or recognized.”

- Essentially HHS definition of UP (except for the caveat that the event would "generally will warrant consideration of substantive changes …”)

# Unanticipated Problem

- UNC definition (per OHRE SOP 6001)
  - "UPs also encompass … information that sponsors are required to report to the FDA in IND Safety Reports under 21 CFR 312.32."
    - "any suspected adverse reaction that is both serious and unexpected … only if there is evidence to suggest a causal relationship" (c)(1)(i)
    - any findings "that suggest a significant risk… Ordinarily, such a finding would result in a safety-related change in the protocol, informed consent, investigator brochure …" (c)(1)(ii and iii)
    - "any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure" (c)(1)(iv)

# Is a single SAE a UP?

- per HHS
  - "OHRP considers adverse events that are unexpected, related or possibly related … and serious [to represent] unanticipated problems because such events always suggest that the research places subjects or others at a greater risk of physical or psychological harm … and routinely warrant consideration of substantive changes
- per FDA
  - "An individual AE occurrence ordinarily does not meet these criteria because, as an isolated event, its implications for the study cannot be understood." Some exceptions:
    - A single occurrence … of a serious, unexpected event that is not commonly associated with drug exposure, but is uncommon in the study population
    - A single occurrence of a serious, unexpected event that is uncommon and strongly associated with drug exposure

# AE or UP?

- Subject in a phase II study of an investigational drug for psoriasis develops severe acute liver failure judged to be related to study drug. IB and ICF list "mild elevation of liver enzymes" as a risk
  - AE since an "untoward medical occurrence associated with the use of a drug"
  - Serious AE since life threatening
  - UP since 1) unexpected, 2) serious, 3) related to the study drug, and 4) would have implications for the conduct of the study. This single event would qualify since it is a serious, unexpected event that is uncommon and strongly associated with drug exposure, and would likely lead to a change in protocol or ICF

# AE or UP?

- Subject in a clinical trial received a dose of an investigational drug that was 5x higher than protocol defined dose. Subject did not develop detectable adverse effect
  - UP (by OHRP definition) since 1) unexpected, 2) related to the research, 3) the subject was placed at greater risk of harm *even though no harm was experienced*, and 4) would probably warrant changes in pharmacy processes …. If the IRB determines the event is serious then this is a UP for FDA also
  - Not an AE since not an "untoward medical occurrence"?

# AE or UP?

- DSMB analysis of clinical trial notes higher than expected risk of stroke associated with investigational drug
  - UP since 1) unexpected, 2) related or possibly related to study drug, 3) serious, and 4) places subjects at greater risk of harm than previously known or recognized
  - Each stroke would probably be a Serious AE

# AE or UP?

- During a behavioral study, a laptop containing individually identifiable information about the sexual activity of subjects was stolen from the investigator's car
  - UP since 1) unexpected, 2) related to the research, 3) places subjects or others at a greater risk of harm than was previously known, and 4) would probably warrant consideration of substantive changes to the investigators processes …
  - Not and AE since not an "untoward or unfavorable medical occurrence"

# AE or UP?

- Subject with advanced pancreatic cancer in a pain management study using hypnosis. During the first hypnosis session, the subject suffers cardiac arrest and dies. Autopsy revealed a massive pulmonary embolism.
  - Serious and unexpected AE; not an UP since unrelated to the study
- Subject getting chemotherapy for leukemia has severe mucositis, which requires hospitalization for pain control and hydration, and subsequent dose adjustment. Risk of severe mucositis is clearly described in the IB and the ICF
  - Serious AE; not UP since not unexpected

# AE or UP?

- During a psychology study evaluating reaction times in response to auditory stimuli, subjects are placed in a small, soundproof booth.  Subject experienced mild claustrophobia and withdraws from the research. ICF discloses the risk of claustrophobia
  - Not UP since not unexpected; AE?

# Case

- Study of adolescent mental health; all participants had preschool psychiatric symptoms. Research Assistant mistakenly emailed a link to 3 participants' surveys (2 of whom were minors) to other participants. Surveys exposed included sensitive information, and identifiers (home addresses, phone numbers, email addresses).

- Is this a UP?

# Is this a UP?

- Was the event "unexpected"?
  - even though "loss of confidentiality is listed in the ICF as a risk of the research, it might be argued that this particular error was unexpected – the CF did not suggest that a mistake by the team would expose the information in this manner
  - if a CF lists death as a possible outcome of use of an anticancer drug (described in the IB as a possible consequence of infection d/t low blood counts) it would not be unreasonable to classify death as a consequence of drug induced cardiomyopathy as "unexpected")

# Is this a UP?

- Is the event "at least possibly related to the research"?
  - yes

# Is this a UP?

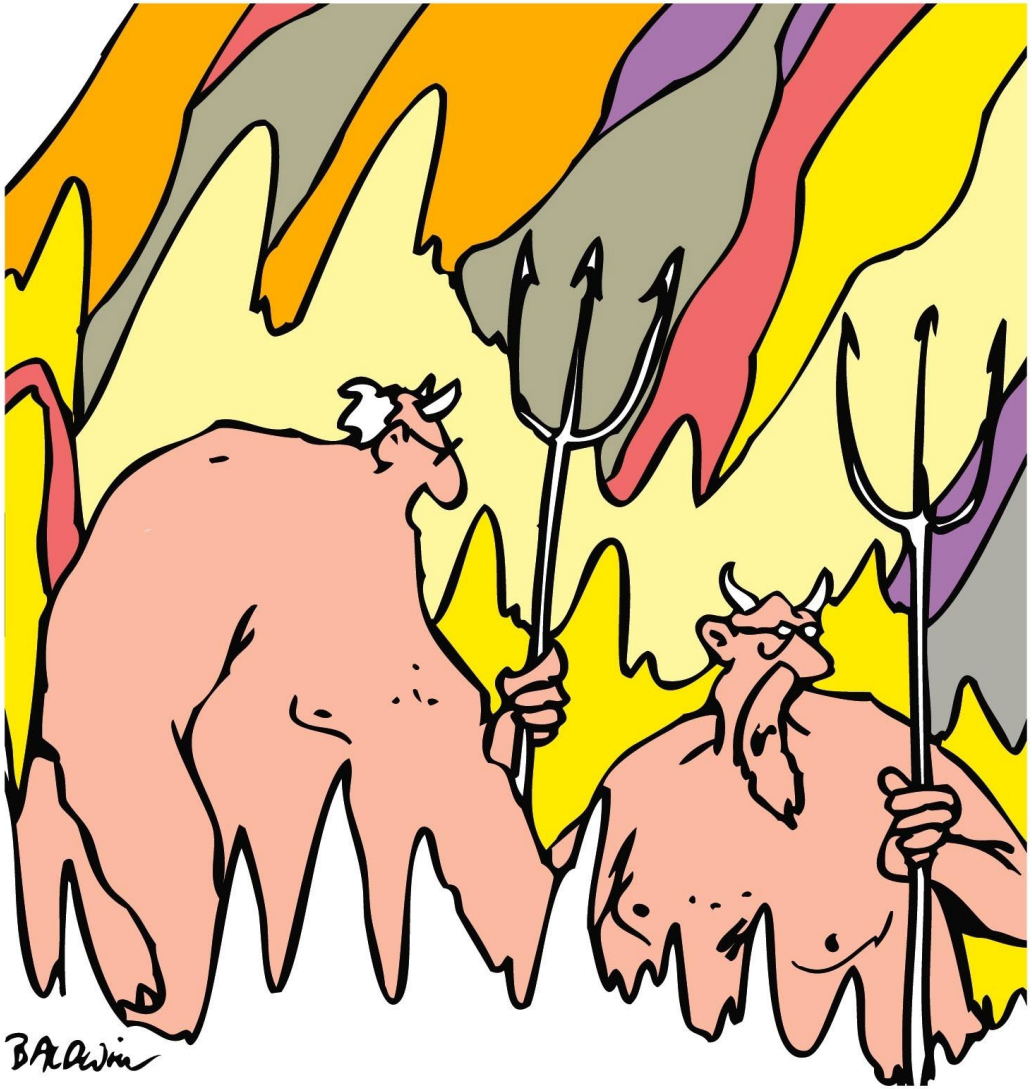
- Were the subjects (or others) placed "at a greater risk of harm … than was previously known or recognized."
  - the IRB certainly considered "loss of confidentiality" in its determination of the R/B. The board's assessment that R/B was acceptable relied on due care by the researchers. This standard, however, was not met, and without that due care there was more risk of harm than the board expected.
  - It also seems likely that participants would have considered the risk to have been minimized thru that same due care by the investigators; thus, the participants' expectation of confidentiality was not met.

# Is this a UP?

- Note also that OHRP is on record as follows:
  - "Example of UPs That Are Not AEs:
  - Stolen unencrypted laptop computer with individually identifiable sensitive information about illicit drug use by surveying college students.“ (K. Borror, 2014)

# Review of AEs and UPs

- Is the R/B relationship still acceptable? Does the research still satisfy 45 CFR 46.111; 21 CFR 56.111?
- Are changes in the study needed to minimize risk?
- Are changes in the consent form needed?
- Do subjects already enrolled need to be re-consented?
- Is the incident an Unanticipated Problem?
- Do other actions need to be implemented to prevent future occurrences?




"You make 23,725 little mistakes,
they never let you forget it."

# Noncompliance

- Noncompliance
  - "Any failure to follow 45 CFR 46 (including any applicable subparts), the requirements or determinations of the IRB or the provisions of the IRB approved research study"
    - "Guidance on Reporting Incidents to OHRP", K. Borror, July 2014]

# Noncompliance

- Noncompliance is a statement of fact
  - failure to follow the protocol, the determinations of the IRB, or the regulations
  - doesn't imply intent or fault
- Noncompliance may be the result of action (or inaction)
  - by the PI
  - by the research staff
  - by the subject
- Noncompliance may be
  - serious or not serious
  - continuing or not continuing

# Noncompliance

- Serious or continuing noncompliance must be reported by the IRB to:
  - OHRP (45 CFR 46.108(a)(4)) and/or
  - FDA (21 CFR 56.108(b)(1))

# Noncompliance

- Serious Noncompliance
  - Regulations do not define "serious"
    - "Non-exempt human subjects research conducted without IRB review and approval or without appropriate informed consent and significant modifications to IRB-approved research without IRB approval is **always serious**"
      - "Guidance on Reporting Incidents to OHRP", K. Borror, July 2014]

- Serious Noncompliance
  - "defined as noncompliance that increases risk of harm to subjects; or adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data or the research." (UNC OHRE SOP 6001)

# Noncompliance

- Serious Noncompliance
  - "an incident that represents a violation of federal regulations, HRPP policies, or the determinations of the IRB which
    - (a) significantly increases the risk to subjects, or otherwise compromises the rights and welfare of research subjects; or
    - (b) appreciably decreases the potential direct benefit to subjects; or
    - (c) compromises the scientific integrity of the research." (UNMC HRPP Policy 8.5)

# Noncompliance

- Serious Noncompliance
  - "The IRB may decide that certain classes or types of non-compliance (for example, protocol violations involving drug dosing errors) represent serious noncompliance." (UNMC HRPP Policy 8.5)

# Noncompliance

- Continuing Noncompliance
  - Regulations do not define "continuing"
    - "Continuing Noncompliance is defined as a pattern of repeated noncompliance which continues after it has been identified that noncompliance occurred, including inadequate effort to take corrective actions or comply with IRB requirements within a reasonable timeframe." (UNC OHRE SOP 6001)

# Noncompliance

- Continuing Noncompliance
  - Regulations do not define "continuing"
    - "(1) repeated incidents of the same or substantially similar noncompliance after the investigator or staff has been notified that the action represents noncompliance or despite appropriate retraining and/or a specific corrective action plan; or
    - (2) repeated incidents of the same or substantially similar noncompliance of such a nature that the investigator should have reasonably been expected to know that such an action was noncompliance." (UNMC HRPP Policy 8.5)

# Case

- Study of adolescent mental health; all participants had preschool psychiatric symptoms. Research Assistant mistakenly emailed a link to 3 participants' surveys (2 of whom were minors) to other participants. Surveys exposed included sensitive information, and identifiers (home addresses, phone numbers, email addresses).

- Is this non-compliance?

# Is this NC?

- "Any failure to follow 45 CFR 46 (including any applicable subparts), the requirements or determinations of the IRB or the provisions of the IRB approved research study" ("Guidance on Reporting Incidents to OHRP", K. Borror, July 2014)
  - The IRB approved protocol included descriptions of protections for the confidentiality of data. There as a failure to follow the protections described (or implied) in the protocol; therefore, this is no.ncompliance

# Is this serious NC?

- Serious noncompliance is "defined as noncompliance that increases risk of harm to subjects; or adversely affects the rights, safety, or welfare of subjects; or adversely affects the integrity of the data or the research." (UNC OHRE SOP 6001)

# Noncompliance vs UPs vs AEs

- NC, UPs and AEs are not mutually exclusive
  - a UP might also be noncompliance if it was the result of someone (investigator, staff, or subject) failing to follow the protocol, the determinations of the IRB, or the regulations
    - loss of an unencrypted computer with PHI on it (probably a UP) might also be noncompliance if the protocol stated that data would only be stored in the cloud or on encrypted devices
    - the IRB would need to decide if the noncompliance was serious or continuing

# Noncompliance vs UPs vs AEs

- Similarly, an AE might also be noncompliance if it was caused by someone (investigator, staff, or subject) failing to follow the protocol, the determinations of the IRB, or the regulations
  - failure to check safety labs that leads to a subject not getting a dose reduction and having an AE as a result might also be noncompliance if the protocol said that safety labs would be checked and doses adjusted accordingly
  - the IRB would need to decide if the noncompliance was serious or continuing

# Review of Noncompliance

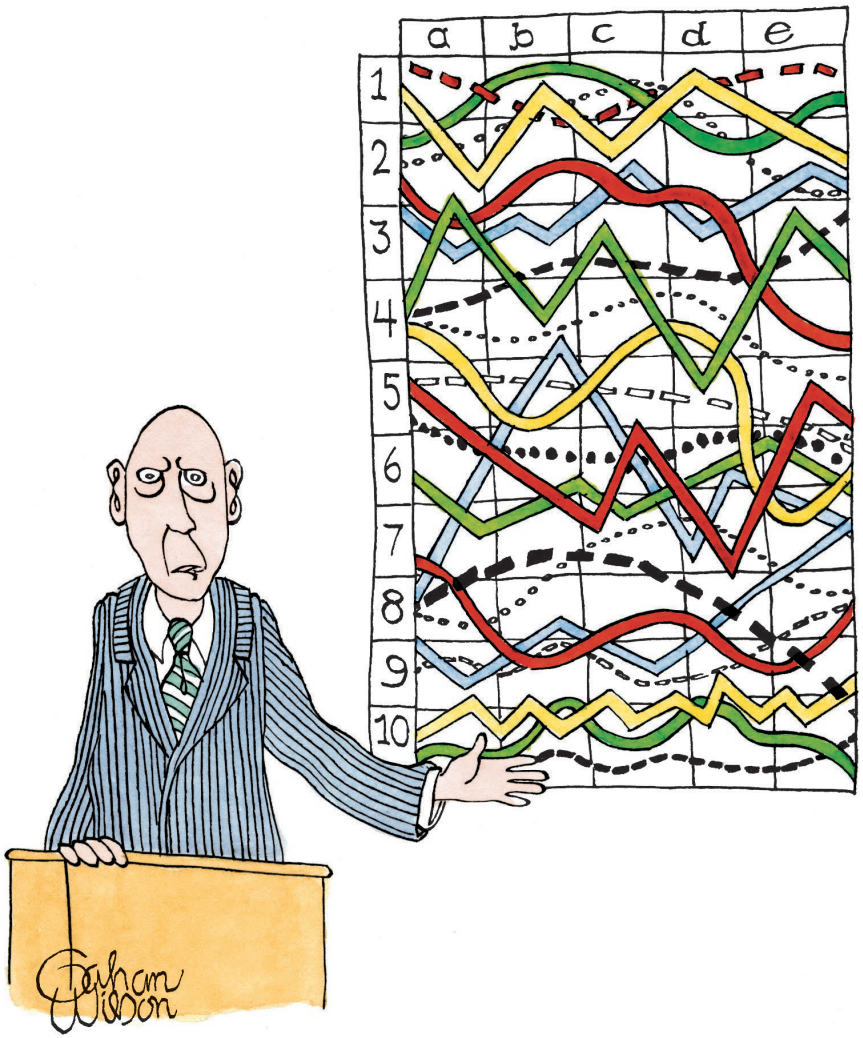
- Is noncompliance serious or continuing?
- Does the noncompliance represent an UP?
- Does the research continue to satisfy criteria for approval at 45 CFR 46.111 and/or 21 CFR 56.111?
- Is the corrective action plan adequate?

# Take home messages

- Not all AEs are UPs; not all UPs are AEs
- In general, to be called a UP, the event must be "serious" enough that a change in protocol or consent is required
- IRB must determine if AE is a UP
- UPs need to be reported; AEs do not

- IRB must determine if noncompliance is serious and/or continuing
- Serious or continuing noncompliance needs to be reported

- Noncompliance, UPs and AEs are not mutually exclusive




*"I'll pause for a moment so you can let this information sink in."*