

PREMISE: We presume that what is occurring in practice is consistent with what was approved by the board. There should be no surprises for the IRB.

The IRB regulation has two similar but separate requirements. One concerns *changes in research* and one concerns *changes in research activity*.

21 CFR 56.108 In order to fulfill the requirements of these regulations, each IRB shall . . .

- (a) follow written procedures:
 - (3) for ensuring prompt reporting to the IRB of *changes in research activity* and
 - (4) for ensuring that *changes in approved research*, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except where necessary to eliminate apparent immediate hazards to the human subjects."

MODIFICATIONS: CHANGES IN APPROVED RESEARCH 56.108(a)(4)

A prospective change in the body of the protocol or an addendum to it.

- Major modifications: any design or goal change or anything that increases risk more than slightly needs full board approval.
- Minor modifications, changes that reduce risk or increase it only slightly. Addition of investigators or devices within protocols approved for such additions are minor modifications.

ACTION: The investigator must submit the IRC modification form (4.32) to the IRB in sufficient time to allow approval. Although IRC will receive and review a modification submitted by the sponsor on behalf of the various investigators, IRC will also need a memo of intent from the investigator. This is to let the IRB know that the investigator has seen the change and has agreed to implement it at that site. A faxed or e-mailed memo will suffice

VIOLATIONS: CHANGES IN RESEARCH ACTIVITY 56.108(a)(3)

NOTE: Violation is not a pejorative word!!!

A failure to follow the protocol rules for one or more subjects. There are two categories of violation.

- **Exception:** permission is granted by the sponsor to make an exception to the protocol to accommodate the needs of individual subjects (example: the protocol requires a visit on day 30 and the subject knows he will be out of town. The investigator seeks an exception to conduct the visit on day 32)
- **Deviation:** A protocol requirement is violated to accommodate an individual without seeking prior permission. (example: the protocol requires a visit on day 30. The subject is ill and cancels the appointment on day 30. The investigator reschedules the visit on day 32.)

ACTION: IRC wants a report on all violations that (a) increase the risk (b) harm the potential for study benefit or (c) have occurred for a second time.

NOTE: THERE IS WIDE VARIATION AS TO USE OF THESE WORDS.

