Coping with Adverse Event Reporting

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Reincarnated and modestly expanded as:

Coping with Adverse Event Reporting

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Workshop 1.02; Thursday Morning

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HHS Reporting Rules: 45 CFR §46

- Under 45 CFR §46.103, “Assuring Compliance”
- Requires written procedures for “prompt” reporting of “any unanticipated problems involving risks to subjects or others”
- Described reporting is to: “the IRB, appropriate institutional officials, and the Department or Agency head”

HHS Reporting Rules: 45 CFR §46

- **Threshold is not specified:**
  - **How big a problem should trigger reporting?**
- **"prompt" is not defined:**
  - **Different time windows would be appropriate for different degrees of severity and probability of recurrence**
- **Reporting to "Department or Agency head" in federally funded research:**
  - **Reasonable inference: reporting to sponsor if *not* federally funded**

HHS Reporting Rules: 45 CFR §46

- **Biggest point:**
  - **The HHS regs require an institution to have written policies to make sure that appropriate reporting of adverse events (and other issues, like noncompliance) get reported to the appropriate places in a timely manner**
  - **Not a lot of detail is provided**
  - **These policies usually are IRB policies; if not, they should be referenced or mirrored in the IRB's written policies and/or written SOPs**

FDA Reporting Rules: 21 CFR §56

- **Under 21 CFR § 56.108 "IRB functions and operations"**
- Requires written procedures for "prompt" reporting of "any unanticipated problems involving risks to subjects or others"
- Described reporting is to: "the IRB, appropriate institutional officials, and the Food and Drug Administration"

Close parallel to the HHS regs; adds FDA to those who must be notified if it is a study of a drug, device, biologic agent or FDA-regulated diagnostic product.

FDA Reporting Rules for Sponsors of Drug Trials: 21 CFR §312

- **Under 21 CFR § 312:32 "IND safety reports"**
- Requires a written safety report of:
  - Any adverse experience associated with the use of the drug that is both serious and unexpected; or
  - Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Described reporting is to: "the FDA and all participating investigators"

FDA Reporting Rules for Sponsors of Drug Trials: 21 CFR §312

- No general statement of timeframe
- If the event is life-threatening or fatal:
  - Must be made by phone or fax ASAP, no later than seven calendar days after the event is reported to the sponsor
- All reports must include analysis of "significance"
- Results of investigations of adverse events must also be reported; there are provisions for late recognition of possible link to study
- Reporting to the IRB is not mentioned here

FDA Reporting Rules for Investigators in Drug Trials: 21 CFR §312

- **Under 21 CFR § 312:52 "Selection of Investigators"**
- Requires that the sponsor select investigators who will
  - satisfy adverse event reporting requirements for FDA
  - promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others

FDA Reporting Rules for Investigators in Drug Trials: 21 CFR §312

- **Under 21 CFR § 312:64 "Investigator Reports"**
- 21 CFR § 312:64(b):
  - Safety reports. An investigator shall promptly report to the sponsor any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately.
- Report is to the sponsor [21 CFR § 312:64(a)]

FDA Reporting Rules for Investigators in Drug Trials: 21 CFR §312

- **Under 21 CFR § 312:66 "Assurance of IRB review"**
  - An investigator shall assure that an IRB that complies with the requirements set forth in part 56 will be responsible for the initial and continuing review and approval of the proposed clinical study. The investigator shall also assure that he or she will promptly report to the IRB all changes in the research activity and all unanticipated problems involving risk to human subjects or others, and that he or she will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

FDA Reporting Rules for Sponsors of Device Trials: 21 CFR §812

- **Under 21 CFR § 812:46 "Monitoring Investigations"**
- 21 CFR § 812:46(b): Unanticipated adverse device effects:
  - A sponsor shall immediately conduct an evaluation of any unanticipated adverse device effect.
  - If the result of the evaluation is that the risk is "unreasonable," "Termination shall occur not later than 5 working days after the sponsor makes this determination and not later than 15 working days after the sponsor first received notice of the effect."
- As with drugs, the reporting to the IRB is elsewhere in the regs, under the investigator's obligations.
- There *is* an IRB reporting requirement for "evaluations"

FDA Reporting Rules for Investigators in Device Trials: 21 CFR §812

- **Under 21 CFR § 812:150(a) "Investigator Reports"**
- 21 CFR § 812:150(a)(1):
  - Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

FDA Reporting Rules for Investigators in Device Trials: 21 CFR §812

- **Special provision for a deviation from the research plan that is made without prior IRB approval (generally because of an emergency):**
- 21 CFR § 812:150(a)(4):
  - Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred.

Same rule for use without informed consent at 21 CFR §812.150(a)(5)

FDA Reporting Rules for Sponsors of Device Trials: 21 CFR §812

- **Under 21 CFR § 812:150(b) "Sponsor Reports"**
  - Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under Sec. 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. 21 CFR § 812:150(b)(1)
  - Reports must be "complete, accurate and timely"

FDA Reporting Rules for Sponsors of Device Trials: 21 CFR §812

- **Under 21 CFR § 812:150(b) "Sponsor Reports"**
  - If a device is recalled or if it is to be destroyed by the investigator, that is also supposed to be reported to the IRB and FDA within thirty working days, and is to include an explanation of what's up.
    21 CFR § 812:150(b)(6)
  - For a significant risk device, a study closure notice to IRB is required within thirty working days
    21 CFR § 812:150(b)(7)

WHO/CIOMS Reporting Guidelines for Adverse Event Reporting in Clinical Research

- **Reminder: The CIOMS guidelines are the World Health Organization's code for the ethical conduct of research.**
- **Appendix 1: A scientifically and ethically sufficient research protocol should set forth** "Methods for recording and reporting adverse events or reactions, and provisions for dealing with complications" (provision 16)

Leaves the details open

ICH Reporting Guidelines for Adverse Event Reporting in Clinical Research

- **Reminder: The ICH (International Commission on Harmonisation) is a body working to make compatible the regulatory structures of several countries.Their guidelines for IRBs state as IRB duties:**

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:

(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects

(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial.

(c) All adverse drug reactions (ADR's) that are both serious and unexpected.

(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

21 CFR §312.32(a): Reportable events in drug studies

Definitions of terms…..

Disability: A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience: Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death.

Serious adverse drug experience: Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Unexpected adverse drug experience: Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure (or analogous information source).

Good News! You have a lot of freedom to set local policy

Bad News! You have a lot of obligation to define local policy

Bad News! You have a lot of obligation to put it in writing

Good News! A lot of the reporting obligation is institutional rather than IRB

Bad News! The FDA puts it under "IRB functions and operations" in their regs

(and we all know where most institutions will put research oversight tasks, anyway)

A Bigger Problem than Defining Local Policy:

- Multiple agencies and multiple contexts lead to a sea of not-quite-concordant reporting obligations;
- CYA response is to report everything to everybody
- IRB gets an absolute deluge of reports, many of which are unlikely to be important to protection of subjects under their wings

Managing the Mess:

- **Set priorities**
- **Recognize the limits of what you can do**
- **Insist on your regulatory entitlement to information that is timely, complete and accurate**
- **Keep subject/patient/participant safety at the top of your list**

Managing the Mess:
Setting Priorities

- **Give intramural events precedence over extramural events:**
  - You're the first IRB and may be the only IRB looking at the event;
  - Giving faith and credence to the AE review of the on-site IRB may do less harm to subjects' protection than does wasting your time on redundant review

Managing the Mess:
Setting Priorities

- **Give precedence to events rated by the on-site investigators as likely to be study-related**
  - These ratings are not very reliable, but you have to decide —full faith and credence notwithstanding—which adverse events you want to look at even though they be from other sites

Managing the Mess:
Setting Priorities

- **Give precedence to events in the same study you're watching, or in studies analogous to ones you're watching**
  - If the disease, dose, route and co-administered drugs are similar to those in a study you're overseeing, the adverse event is more likely to be important for your subjects than if the study generating the AE is totally different from the one you're watching

Managing the Mess:
Setting Priorities

- **Give precedence to life-threatening events**
  - No-brainer
- **Give precedence to studies without formal safety monitoring**
  - Especially single-investigator, investigator-initiated IND, locally-produced drug or device; you may be in effect the whole safety monitoring program (not a good thing)

Managing the Mess:

- **Recognize the limits of what you can do**
  - Implied in the foregoing slides
  - You cannot meaningfully review 12 AE reports per day for every IRB member and staffer (the numbers are even bigger for some IRBs)
  - Your review adds little if you don't know the numerator or the denominator
  - Your review usually adds little to that of your colleagues at another IRB, and you *can* grant them faith and credence
  - Your goal should be to triage such that you can quickly decide whether the report changes the risk/benefit balance or the consent burden for subjects in studies under your watchful eyes

It is entirely within an IRB's authority to say, for example:

"Because of this adverse event, we no longer are assured of the adequate protection of the subjects/patients enrolled in this study. Until the concerns raised by this event are resolved, this IRB's approval of the study is suspended. No new subjects may be enrolled after the date of this notice. Subjects currently enrolled and receiving the study drug may (bzw. may *not*) continue to receive it."

Managing the Mess:

- **Keep subject/patient/participant safety at the top of your list**
  - **This is another "no-brainer"**
  - **But we're all compulsive enough to worry about what might happen if we miss something**
  - **We should follow that compulsion well enough to build a good triage system**
  - **But we should also remember that enormous mind-numbing tasks, repeating work of other IRBs, are taking us away from tasks that have far more safety value**

Sponsors and Investigators: *they can help control the damage*

- Identify adverse events that are likely
- Establish expected occurrence rates
- Craft a monitoring plan for determining when those expected rates are being exceeded
- Change “unexpected” AEs into expected ones
- Allow periodic summary reporting rather than individual reporting

Example: *Severe GVH:*

- **We expect 35% of patients in this protocol to have GVHD; we expect 15% to develop Grade III or Grade IV GVHD**
- **80% confidence limits for those rates by number of enrollees are set forth in Table 2.**
- **If those rates are exceeded (on q-90-day review), excess GVDH will be reported as an adverse event.**
- **If GVHD incidence remains below the limits set in Table 2, it will be reported in summary form in periodic reports, but will not be reported separately.**

Example: *Death in salvage Rx:*

- **We expect 70% of patients qualifying for this protocol would die within six months if treated according to conventional (supportive) care.**
- **We hope the treatment given in this protocol will prolong life and therefore decrease the number of deaths in six months of follow-up.**
- **We will therefore not consider deaths on this protocol automatically to represent study-related adverse events.**
- **The algorithm by which we will identify excess deaths or unusual deaths as study-related adverse events is set forth in Table 3.**

Sponsors and Investigators: *they can help control the damage*

- Identify protocol deviations that are likely
  - BMT: too much prior radiation for TBI
  - Chemo: allergy to allopurinol
  - Compassionate use in protocol near-fit patient
- Establish responses to those scenarios
- Make them a part of the protocol
- Voilá! They're now not deviations!

Overarching Theme

Carefully thinking about likely adverse events and likely protocol deviations can allow them to be addressed prospectively in the protocol that the IRB reviews.

This can save *everybody* a lot of headaches.

A handout version of this presentation may be obtained from my ftp site at the University of Minnesota:

http://www.tc.umn.edu/~hamme001/SAE.HO

The site-posting will be maintained for a minimum of thirty days after the meeting.

Dale Hammerschmidt, M.D.