Regulatory Considerations and Adverse Event Reporting

C. Michael Gibson, M.S., M.D.

Harvard Medical School

Chairman, PERFUSE Study Group

Founder and Chairman, WikiDoc & WikiPatient, The World's Open Source Textbook of Medicine Viewed 896 Million Times A Year

Acronyms Used

- AE - Adverse Event
- ADE- Adverse Device Effect
- CFR - Code of Federal Regulations
- CRF - Case Report Form
- IDE - Investigational Device Exemption
- IRB - Institutional Review Board
- GCP - “Good Clinical Practice”
- NSR - Non Significant Risk

Unanticipated ADE Definition per CFR part 812.3(s)

- Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem or death was not previously identified in nature or severity, or degree of incidence in the investigational plan or application . . ., or any other unanticipated serious problem associated with a device that relates to the rights, safety or welfare of subjects.

Why Is All the Fuss About AEs?

- The Sponsor, the Investigator, and the Institution conducting the clinical study must comply with very specific government regulations.
- The primary intent to protect patients' safety and welfare during the conduct of a clinical study can only be met by accurate, timely reporting of AEs.

FDA Routinely Reviews AE Reporting When Auditing

- Reviews the FDA and IRB notification timelines from correspondence files
- Will note if there are any unreported AE(s) from chart review
- Will review sponsor notification to investigator of AEs

FDA Bioresearch Monitoring Program

- This is an active program which generates several warning letters each month for clinical investigators, IRBs, and sponsors
- Both IDE and NSR studies are audited by FDA investigators
- The local IRB often becomes a target for FDA when an NSR study is inspected

FDA Bioresearch Monitoring Program (cont'd)

- FDA will search for unreported AEs by reviewing the CRFs and medical records.
- Clinical investigator preparation and the quality of the documentation become critical issues.

FDA Bioresearch Monitoring Program Manual

- Specific instructions to FDA investigators:
  - "Pay particular attention to events reported from clinical sites. Determine if these were relayed to FDA as required."
  - "Describe the sponsor's method or system for tracking adverse reactions and for relaying information of adverse experiences to participating investigators".
  - "Obtain copies of any notification to investigators relating to adverse experiences".

Examples of FDA Warning Letters Regarding AEs

- No documentation that AE was reported to sponsor
- Reoccurrence of AE was not mentioned at the follow-up visit, AE required intervention
- Death of subject was not reported to local IRB or sponsor
- Patient deaths occurred within three months of surgery and not reported to FDA as stated in protocol

More Examples of FDA Warning Letters Regarding AEs

- Investigator failed to report unanticipated AE to IRB, failed to report within the required 10 days
- Two patients experienced the same AE, however, only one was reported
- AE not immediately reported and reported inaccurately
- Death of study subject was reported to local IRB two years after death occurred

Sponsor Strategies to Improve AE Reporting

- Educate the investigator and support staff of the AE reporting requirements as specified in the protocol (discuss at investigator meeting/coordinator meeting).
- Review the AE reporting procedures and completion of the CRF at the pre-study or study initiation site visit.
- Review AE reporting during each monitoring visit.

Adverse Event Reporting Time Line

- Identified Adverse Event
- Is Event Serious and Associated with Device and Not Specified in Protocol (unanticipated)?
  - NO = Stop and complete AE CRF
  - YES = Investigator has 10 working days to report the UADE to both Sponsor and own IRB

AE Reporting Time Line (continued)

- From the time the Sponsor becomes aware of a UADE, they have 10 working days to determine if the AE poses unreasonable risk to study subjects
  - NO = Reports to all IRBs, all Investigators, and FDA
  - YES = has 5 working days to Terminate the Study and Report to all IRBs, all Investigators, and FDA

So Why All The Fuss?

- Because It Is ***The Law***

- Because It ***Protects*** Our Patients Who Ultimately Could Be Our Family or Friends

References

- FDA Bioresearch Monitoring Compliance Program Guidance Manual (7348.810)
- International Conference on Harmonization, Draft Guidance on “Good Clinical Practice”
- 21 CFR, part 56 (Institutional Review Boards)
- 21 CFR, part 803 (Medical Device Reporting)
- 21 CFR, part 812 (Investigational Device Exemptions)
- 21 CFR, part 821(Medical Device Tracking Requirements)