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Answers That Matter.

Eli Lilly and Company
Vish S. Watkins, MD
Hunter Heath III, MD

Reporting of Adverse Events to Institutional Review
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Answers That Matter.

Adverse Event Reporting – Current Concerns Of IRBs Identified By FDA

- Volumes of Adverse Events (AEs) Received By IRBs
 - Large volumes of information including individual adverse event reports (12,000/yr in some cases)
 - Range from serious to relatively minor ones from investigators and sponsors (usually via investigators)
 - In some cases both anticipated and unanticipated events are reported
- Quality of AE Information
 - Individual AEs not informative enough to permit IRBs to assess implications
 - Blinded reports cannot be assessed
 - Difficulty in reviewing and interpreting significance of large volumes of individual unaggregated and unanalyzed reports

FDA Question– Role of IRBs In Review Of Clinical Trial AEs

- IRB Role – 21 CFR 56.109 and 56.111
 - Approve research on basis of reasonable risk:anticipated benefits for subjects
 - Ensure appropriateness of Informed Consent Documents
 - Ensure that research plan has adequate provision for data monitoring
 - Continuing review at intervals appropriate to the degree of risk
- Investigator Role –21 CFR 312.66
 - Report to IRB...changes in research activity and all unanticipated problems involving risk to human subjects...
- Sponsor Role – 21 CFR 312.56
 - Review and evaluate evidence relating to safety...reports to FDA...
- The optimal solution would:
 - require no change in the current Federal Regulations regarding IRB role
 - maintain the roles of sponsors, investigators, and IRBs in assessing potential changes to the risk:benefit of the research based on safety findings during the clinical trial

Proposed Framework For Solution:Key Principles And Processes

KEY PRINCIPLES

- Effectiveness without complexity
- Timely communication to regulators, investigators, and IRBs of safety findings that change risk:benefit of the research
- Consistency with existing regulations and guidelines from ICH, CIOMS

KEY PROCESSES

- Expedited AE reporting to regulatory agencies of significant individual SAEs
- Stop the flow of AE reports to IRBs and investigators whose volume and quality do not enable them to assess risk:benefit changes to the research
- Provide information to investigators and IRBs in a comprehensible format that enables them to assess risk:benefit changes

Approaches To Providing AE Information To IRBs

- Goal is to provide IRBs and investigators with information that is cohesive, concise, and sufficient to enable them to assess significant safety signals or adverse effects that arise during clinical trials that could potentially change risk:benefit of the research
- A draft of the CIOMS VI Working Group Report whose publication is imminent provides a framework in Chapter 7 that addresses many of the questions raised and provides suggested solutions
- The following slides provide a framework upon which a solution could be developed

Suggested Approach – Types of AEs IRBs Should Receive

- Sponsors continue expedited reporting of serious, unexpected ADRs to regulatory agencies – but harmonize process across regulatory agencies and follow ICH Guideline E2A
- Eliminate the current practice of routine expedited case reporting to both investigators and IRBs
- Communicate selected alert reports to investigators and IRBs on the basis of clinical judgment, the seriousness of the event, strength of the evidence for causality, and impact on safety
 - Examples would include serious hepatotoxicity, aplastic anemia, fatal or life-threatening anaphylaxis

Suggested Approach - Providing Information To IRBs

- Provide periodic (e.g., quarterly) summary reports of safety to IRBs that include
 - A line listing of SAEs that were sent in an expedited manner to regulatory agencies
 - Line lists should include only expedited reports from clinical trials
 - A summary assessment of the safety profile of the drug based on the above information including significant individual AEs and aggregated data analyses
- If a significant safety finding is discovered from an individual case or from aggregated data, the sponsor should promptly notify regulatory agencies, investigators, and IRBs
 - A significant finding is one that is relevant to care of the patient or has a significant impact on the course of the clinical trial, the clinical plan or program for the compound, or the informed consent