FDA Safety Reporting Requirements for Clinical Trials: Tips for Compliance
“New” Rules Effective 28 September 2011

Mukesh Kumar, PhD RAC
Senior Director, Regulatory Affairs
Amarex, Germantown, MD, USA
mukeshk@amarexcro.com
Prepared for ACRP live webinar on September 20, 2011.

Disclosure

The presenter(s) for today’s session:

Dr. Mukesh Kumar

I have no relevant financial relationship in connection with this educational activity.
Objectives

Upon completion of this webinar, you should be able to:

1. List key additional obligations in the new rules and be able to understand the rationale behind the changes in requirements.
2. Revise safety reporting procedures to address classification of adverse event, expanded role of investigators and sponsors, and time-lines for reporting to IRB and FDA.
3. Define new training requirements for all personnel, understand key FDA concerns and prepare for FDA queries and audits.

Where Are You?
Agenda

• Regulatory requirements for safety events
• Definitions and practices
• Safety Reporting processes
• Safety Database
• Role of Investigators and Sponsors
• Current Practices
• Role of IRBs
• Do’s and Don’ts of adverse event reporting

Safety is the Most Important Aspect of a Drug

• A new drug can have unintended negative effects
  – Due to the way the drug acts
  – Its interactions with the patient’s physiological and psychological profile
  – Its interactions with other drugs that the patients might be taking
  – Its interactions with the dietary profile of the patient
• Marketing approval of a drug is based on the balance between risk and benefit
• Safety is very important post-marketing as well
What is an Adverse Event (AE)?

- Any *untoward* medical occurrence (unintended negative effect) *associated* with the use of a drug whether or not considered drug related
- Could be due to any use (off-label, combination), route of administration, formulation or dose
- When confirmed to be drug-related, it is “Adverse Drug Reaction (ADR)”

Associated vs Related

What is an Adverse Event?

- Any unfavorable or unintended sign, including:
  - Symptoms or diseases
  - *Worsening* of a baseline condition
  - Abnormal lab findings
  - Protocol-defined events
- AEs define the safety profile for an investigational drug
- The primary goal of an IND to find if the drug is safe (and effective)
Why is it Important to Track all AEs?

- Help timely mitigation of serious harm to study participants
  - Individual AEs
  - Cumulative review of all AEs
- Benefit from experience with other similar approved and investigational products
- Decision to revise or terminate a clinical study
  - Develops accurate drug toxicity profiles
  - Compliance with regulatory requirements

Regulatory Requirements for Reporting AEs

- AE reporting is required for clinical studies under 21CFR312.32
- All AEs need to be reported
  - Most as a cumulative periodic report (annual)
  - “Interesting” ones immediately
- AE reports must be complete
- Most FDA urgent queries are regarding AEs
- FDA is a safety-centric organization
FDA: “There are errors in AE Reporting”

- Regulation is vague, leading to misinterpretation
  - Associated with the use of drug
  - Reasonable possibility of drug relationship
- Sponsors take a over-cautious approach leading to unnecessary expedited reports of AEs to the FDA
  - SAEs likely due to underlying disease
    - Death in late-stage cancer disease
  - SAEs due to the population
    - Stroke or AMI in elderly population
  - SAEs that were study endpoints
    - Endpoint is whether the drug reduces the rate of event

Overuse of Expedited Reporting is Counter-Productive

- Do not meaningfully help in safety monitoring by regulators
- Do not meaningfully contribute to developing the safety profile of the drug
- Drain resources at the FDA, investigators and IRBs
- Does not meet the intent of the regulation
Polling Question #1

FDA’s New Rule and Guidance

• Well-established practices at the FDA over the last two decades
  – FDA practice since 1990s
  – Federal register notice, 14 Mar 2003
    • Draft Rule to amend 21 CFR 312.32
  – FDA comments to IND safety reports
• Final rule released on 29 Sep 2010, effective initially on 28 Mar 2011, extended to 28 Sep 2011
• Draft Guidance document released on 29 Sep 2010
• Improve quality of safety reporting, help FDA with critical safety monitoring, and harmonize with EMA, ICH E2A and other regulatory agencies
Purpose of the New Rule

- Clarify definitions of adverse events with regards to expectedness, relatedness and seriousness
- Use internationally acceptable definitions and standards
- Revise requirements for expedited reporting
- Clarifies circumstances for un-blinding ongoing study
- Clarifies format and frequency of reporting
- Clarify FDA- and IRB-reportable adverse events to minimize “noise”
- Make BA/BE studies subject to IND safety reporting requirements

AE Management is Multi-Dimensional

- How will I describe the AE?
- Is this AE also a Serious AE (SAE)?
- How will I grade the severity?
- What is the relationship of the AE to the study product?
- Has this AE been previously reported with this participant?
- Will this AE affect the participants study product dosing?
- Did the participant receive any treatment?
- How will I document this event?
- How and to whom will I report this event?
Common Terms to Define AEs

- **Associated** with drug
  - Happens after drug intake
  - The cause for the AE is not confirmed
- **Related** to drug
  - Caused by drug intake (Adverse Drug Reaction)
- **Suspected** adverse drug reaction (SADR)
  - Known drug effect based on past history
  - Most-likely due to drug intake
- **Expected** adverse drug reaction
  - Should happen upon drug intake
  - At a known frequency and grade of seriousness
- **Unexpected** SADR
  - New event not known for this drug
  - Most likely caused by the drug

Grading AEs

- **Seriousness**
  - is a method of labeling an adverse event when an event meets certain criteria
  - This type of evaluation is *subjective*
  - Based on investigator and/or subject assessment
- **Severity** (also known as intensity)
  - describes the event in “measurable” terms, defined as grade of the adverse event (Grade 1-5)
  - This type of evaluation is *objective*
Serious Adverse Event (SAE)

An AE that at any dose
- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongs hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or birth defect
- Important medical event
- Other conditions as specified in the protocol

Revised Definitions

- Suspected Adverse Drug Reactions
  - Evidence to suggest causal relationship
  - Requires judgment by the investigator and sponsor
- Unexpected Suspected Adverse Drug Reactions
  - Not listed in the Investigator’s Brochure
  - Not consistent with the available risk information
  - Not known to occur with the drug being tested
- Serious Adverse Drug Reactions
  - Grade 3-5 AEs
  - Both investigator and sponsor should assess
  - Sponsor’s assessment considered critical
  - If either sponsor or investigator assesses the AE to be SAE, it should be considered an SAE
Grading the Intensity of an AE

- The intensity of all AEs must be grades on a linear scale
  - Grade 1: Mild AE
  - Grade 2: Moderate AE
  - Grade 3: Severe AE
  - Grade 4: Life-threatening or disabling AE (hospitalization)
  - Grade 5: Death related to AE
- AEs of grades 3-5 are generally SAEs
- Grade 1-2 AEs could lead to SAEs if the frequency is higher than expected

Polling Question #2
AE Reporting Process

- All Adverse Events must be assessed by investigator for
  - Relationship to the study product/procedure
  - Severity of the event (i.e., grade)
  - Seriousness of the event (AE or SAE)
- Based on the above the Investigator must decide if expedited report is required
- The investigator must inform the sponsor if expedited report is deemed required
- Detailed information must be collected
- All AEs must be recorded
- AEs must be managed immediately to address subject treatment/comfort

Documenting AEs

- The following should be recorded for all AEs
  - Name of this event
  - Start/stop date/time
  - Any treatment for the event
  - Intensity (mild, moderate, severe)
  - Relationship of event to study drug
    - action taken with study drug
  - Outcome, resolution
  - Was the event expected
Reporting Adverse Events

- Investigator is responsible for
  - Recording the AEs on protocol-specific documents (CRFs)
  - Collect and store all supporting source documents
  - Report SAEs to the sponsor
  - Consult with sponsor regarding IRB reporting

- Sponsor is responsible for
  - Review and assess SAEs for expedited reportability
  - Report to FDA and assist with reporting to IRBs
  - Maintain Safety Database to conduct cumulative assessment of all AEs

Polling Question #3
Importance of the Safety Database

- Collection of all AEs, serious or not
- All SAEs must be evaluated in the context of all previously reported related AEs using safety database
- Aggregate analysis must be conducted if several similar adverse events are reported
- IND Safety Reports must be submitted only when the SAE meets all three conditions
  - Suspected adverse drug reaction
  - Serious
  - Unexpected

Avoid Over-Reporting of IND Safety Reports

- Better description of safety reporting procedures in the protocol
  - Anticipated adverse events based on the study population, natural progression of the disease, background event rates, co-morbid conditions, and past experience
  - Safety monitoring processes
- Evaluate each unexpected AE for causality
  - Evidence for causality
  - FDA wants the investigator and sponsor to use judgment
- Periodic aggregate analysis of all AEs
  - During IND Annual report
  - Special events, e.g., interim analysis, DSMB review
Additional Tips for Better AE Reporting

• Adequate Investigator’s Brochure
  – Document non-clinical and clinical safety information
  – Possible risks and side effects based on the drug
  – Precautions and special monitoring required for the study
• Update Investigator’s Brochure
  – New preclinical and clinical information
  – New publications and research reports
• Installing independent sponsor medical monitor
  – Review all AE and SAE reports
  – Discusses with the investigators
  – Provides sponsor’s assessment
  – Create IND Safety Reports

IND Safety Reports

• All available information on the SAE
  – Test reports and notes
  – Assessment of causality
  – Narrative of event
• Could be FDA 3500 or CIOMS format
• Could be sent via email to the IND project manager
• Follow-up IND safety report, as needed.
In Conclusion

- Adequate protocol design and Investigator’s Brochure
- Establish separate safety monitoring and reporting processes
  - Independent safety monitor
  - Safety Database
  - Safety monitoring plan
- Train investigators and personnel
- Adequate monitoring
- Careful review of SAEs and AEs before reporting
- When in doubt, report to FDA

Questions

- To Submit a Question:
  - Use the Q & A Panel in the lower right-hand corner of your screen to type your question.
  - Any unanswered questions will be handled by email after the session.
Evaluation and Contact Hours

• Continuing education credit is available to all purchasers with the completion of an evaluation form
• The evaluation form will be available tomorrow.
• Log into your ACRP record and go to the “Tests, Evaluations, and Certificates” section.
• You have until October 20, 2011 to complete the evaluation form and receive 1.5 contact hours
Thank you for listening to ACRP Webinars

We value your feedback.
Please complete the WebEx post-event pop-up survey (non-credit) or the ACRP online evaluation form on your “My Tests, Evaluations, and Certificates” page (for credit).

Visit www.acrpnet.org
for future webinars