Sponsor/Sponsor-Investigator Drug Safety Reporting Responsibilities AND Changes to Policy on Investigator Safety Information Reporting to IRB

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What Changed?

- FDA Regulations regarding IND safety reports from Sponsors/Sponsor-Investigators to FDA.
- IRB Policy on Investigator reporting of safety information to IRB – change based on FDA Guidance.

SPONSOR/SPONSOR-INVESTIGATOR DRUG SAFETY REPORTING TO FDA, INVESTIGATORS & IRB

Who is Affected?

- Sponsors
  - Flow down to Investigators
- Sponsor-Investigators (SI)
  - Impact on multi-site trials

What Didn’t Change? (yet)

- Device safety reporting obligations.

Premise Underlying New FDA Regulations

- Sponsor is in the best position to collect safety information from multiple sites, other clinical studies in humans and animal and in vitro studies.
- Sponsor has responsibility to analyze this information and make reports to FDA, investigators and IRBs.
- Single adverse event reporting without analysis generally is not useful.

What's Required from Emory SI?

- Rapid collection of safety information from all study sites and other entities.
- Full analysis of safety information.
- Determining if there is increased risk to subjects.
- Reporting Serious Unexpected Adverse Reaction to FDA & all investigators.
- Reporting to Emory IRB with identification of unanticipated problems.
- Submission of appropriate modifications to protocol, etc.

Definition:
Adverse Event

- Definition: Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

New Term:
Suspected Adverse Reaction

- Definition: Any Adverse Event for which there is a Reasonable Possibility that the drug caused the Adverse Event.

Definition: *Serious*

- Definition: An Serious Adverse Event or Serious Suspected Reaction is one that results in –
- Death
- Inpatient hospitalization
- Prolongation of hospitalization
- Persistent or significant incapacity
- Substantial disruption of ability to conduct normal life functions
- Congenital anomaly/birth defect
- Based on appropriate medical judgment, event jeopardizes subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Definition: *Unexpected*

- Definition:
  - Event/reaction not listed in investigator brochure (IB); or
  - It is not listed in IB at specificity/severity that has been observed; or
  - If no IB, event is not consistent with risk information in protocol or elsewhere in FDA application; or
  - It is mentioned in IB as occurring in class of drugs or anticipated from pharmacological properties of drug, but is not specifically mentioned as occurring with the particular drug being investigated.

Other Important Terms

- *Life-Threatening:* places subject at immediate risk of death.
- *Reasonable Possibility*: evidence suggests causal relationship between drug being investigated and Adverse Event or Adverse Reaction.

What Sponsor Must Regularly Collect & Promptly Review

- All reports of Serious Adverse Events from all investigators.
- All reports of Non-Serious Adverse Events from all investigators.
- Information on safety of drug from sources inside and outside US, including information from clinical investigations, epidemiological investigations, animal studies, & in vitro studies,
- Information from published scientific literature and unpublished scientific papers.
- Reports from US regulatory authorities.
- Reports from non-US regulatory authorities.
- Reports of non-US marketing experience for drugs not marketed in US.

Required Forms & Follow-Up

- Sponsor needs to have forms investigators can use for immediate recording/reporting of any Serious Adverse Event, whether or not event is considered drug related.
- Form must include section for assessment of whether there is a Reasonable Possibility that drug caused event.
- Sponsor also needs form and timetable for investigator reporting of Non-Serious Adverse Events.
- Sponsor must train investigators on how to use forms.
- Sponsor must follow-up on all forms and safety information received.

Required Reporting to FDA & Investigators

- Sponsor/S-I must report in IND Safety Report:
  - Serious and Unexpected Adverse Reaction Includes:
    - Single occurrence of uncommon event known to be strongly associated with drug exposure.
    - One or more occurrences of uncommon event known to be strongly associated with exposure to drug and is uncommon in study population.
    - Aggregate analysis of specific events seen in CT that indicates events are occurring more frequently in drug treated group.

Required Reporting to FDA & Investigators

- Sponsor/SI must report via IND Safety Report:
  - Findings from ANY epidemiological studies, clinical studies or analysis of multiple studies that suggest significant risk in humans exposed to drug.
  - Findings from ANY animal or in vitro testing that suggest significant risk in humans exposed to drug.
  - Increased rate of Serious Suspected Adverse Reaction over that listed in IB or protocol.
  - Study endpoints that are a Serious and Unexpected Adverse Event (SUAE) when there is evidence suggesting a causal relationship with drug being investigated.

Follow-Up IND Safety Reports

- Sponsor must send Follow-Up IND Safety report to FDA and to all investigators with any additional information developed during follow-up investigation.
- Follow-Up report must be provided as soon as additional information is available.

Persons/Entities that Must Receive Report & Timetable

Event	Report to:	Form	TIme
Serious, Unexpected, Suspected Adverse Reaction (including endpoints that are SUSARs). Must have AE + Causal Relationship with Drug	•FDA •All investigators •Emory SI – Copy Emory IRB	Form 3500A or narrative format – label "IND Safety Report"	15 calendar days after determining reportability
Findings from Other Studies that Suggest Significant Risk	•FDA •All investigators •Emory SI – Copy Emory IRB	Narrative format – label "IND Safety Report"	15 calendar days after determining reportability
Increased rate of Serious Suspected Adverse Reaction	•FDA •All investigators •Emory SI – Copy Emory IRB	Narrative format – label "IND Safety Report"	15 calendar days after determining reportability
Unexpected Fatal or Life Threatening Suspected Adverse Reaction	•FDA •All investigators •Emory SI – Copy Emory IRB	Form 3500 A or narrative format – Label "IND Safety Report"	7 cal. days after initially receiving information on event

Event Later Determined to be Reportable

- If Sponsor determined an event did not need to be reported to FDA/investigators, but later determined it should have been reported, then:
  - Sponsor has to make report no later than 15 days after determining report should be made.

Emory Sponsor Investigators – Analysis Required for Emory IRB

- Include analysis as to whether Adverse Events, or other safety information, from Emory sites or sites outside of Emory constitute Unanticipated Problem Involving Risks to Subjects or Others.
- Include description of any changes required to protocol, etc. and submit appropriate modifications to IRB.

Changes to Policy on Investigator Safety Information Reporting to IRB

Major IRB Reporting Requirement: Unanticipated Problems (UPs)

- IRB must report UPs involving risks to subjects or others to institutional officials and regulatory agencies.
- Some adverse events are UPs, and others are not.
- Adverse Event = UP if: Unexpected + Serious + Related or Possibly Related to Participating in Research

Special Rule for FDA Regulated Trials

- AE = UP ONLY IF:
  - Single occurrence Serious, Unexpected Adverse Event (SUAE) that is uncommon and strongly associated with Test Article
  - Single or small number of occurrences of SUAE that is not commonly associated with Test Article but is uncommon in study population
  - Multiple occurrences of AE that based on aggregate analysis shows AE were not just isolated occurrences and involve risks to subjects.
  - AE described in IB but at clinically significant increased rate over what was expected.
  - Any safety finding that would cause modification to IB, protocol or informed consent or prompt action by IRB to ensure subject protections.

Investigator Reporting Requirements – Internal Adverse Events

- All adverse events that take place at Emory or at sites under jurisdiction of Emory Sponsor-Investigator that constitute UPs must be reported to IRB. Must include any analysis of why AE = UP.
  - Emory IRB makes final UP determination and reports to regulatory agencies and institutional official.

Investigator Reporting Requirement – External Adverse Events

- Emory IRB will rely on sponsor to analyze events occurring outside Emory to determine which AEs constitute UPs. Report from sponsor should include UP analysis and designation. If Sponsor does not provide UP designation, IRB will request it from sponsor or make its own.
  - Emory IRB will rely on IRB at site where event occurred to report to regulatory agencies.

Questions

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