Adverse Events: Refresher and Updates

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Disclosures

• Employee: Avid Radiopharmaceuticals, Inc.
Objectives

At the conclusion of this discussion, participant will be able to:

– Describe FDA’s 9/29/2010 final rule regarding adverse event (AE) and serious AE reporting

– Define the following terms: adverse event (AE), suspected adverse reaction, adverse reaction, serious, life-threatening

– Apply the AE and serious AE regulations to common scenarios in medical imaging clinical trials

– List resources for further information on the topic of AE and serious AE reporting
Purpose of the New Rule

• Improves consistency with the International Conference on Harmonization (ICH) recommendations

• Help sponsors decide whether an AE is related to the investigational product

• Streamlines IND safety reporting to FDA and IRB

• Clarifies timeline and content for expedited reporting of serious AEs

• Improve patient safety by ensuring that critical information is reported in a timely manner
FDA Final Rule on AE Reporting

September 29, 2010: 21CFR Parts 312 and 320

- Incorporates new definition for AE
- Incorporates new definition for serious AE
- Incorporates new reporting requirements
- Impacts how & what investigators report to IRB
- Impacts how & what sponsors report to FDA

Effective: March 28, 2011

Draft Guidance Document Published for Comment Sept 2010
### Previous

| **Adverse event:** No definition in CFR |
| **ICH definition:** Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have a causal relationship with this treatment. |

### After March 2011

| **Adverse Event:** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. |
| An adverse event can arise from any use of the drug (e.g. off-label use, in combination with another drug) and from any route of administration, formulation, or dose, including an overdose |
Subsets of Adverse Events

• Suspected Adverse Reaction:
  – Any AE for which there is evidence to suggest a causal relationship (reasonable possibility) between the drug and the AE
  – Implies a lesser degree of certainty about causality than adverse reaction

• Adverse Reaction:
  – An adverse reaction means any AE caused by a drug
What is the AE reporting period for this drug?
- Incorporates physical and biological clearance
  - For an F-18 tracer, the reporting period may be 24 hours
  - For an I-131 antibody with a long biologic half-life, the reporting period may be 30 days

The sponsor will provide you with the AE reporting period.

The protocol may require a follow-up visit or contact to assess for AEs at the end of the reporting period.

**REMEMBER:** an AE is temporally associated with the drug, not necessarily *caused* by the drug
Is this an AE?

• Your patient complains of shoulder pain after being under the scanner with her arms up for one hour after the injection of an investigational imaging agent.

• Your patient comes to the imaging department 24 hours after chemotherapy. He complains of mild nausea 45 minutes after being injected with the investigational tracer.

Just because you don’t think an AE is *caused* by the imaging agent, does not mean it shouldn’t be *recorded* and thereby reported to the sponsor!
Expected vs Unexpected

- **Unexpected:**
  - When the AE is:
    - not listed in the investigator brochure
    - not listed at the **specificity** or **severity** that is being observed
      - Specificity: cerebral thromboembolism or cerebral vasculitis when IB lists “cerebral vascular accidents”
      - Severity: hepatic necrosis when the IB only lists “elevated hepatic enzymes”
    - not consistent with the risk information described in the general investigational plan or elsewhere in the current application (in the absence of an investigator brochure)
    - listed as occurring with a class of drugs…but not specifically mentioned as occurring with the particular drug under investigation
      - Angioedema anticipated in ACE Inhibitor class of drugs
# AE Case Report Form: Sample

## ADVERSE EVENTS

List any adverse event with onset after administration of I-131-CLR1404 through the end of the study including worsening of pre-existing conditions.

<table>
<thead>
<tr>
<th>AE #</th>
<th>Adverse Event (one event per line)</th>
<th>Onset</th>
<th>Resolution</th>
<th>Action Taken</th>
<th>Relationship to Study Drug</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adverse Event (one event per line)</td>
<td>Onset</td>
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</tbody>
</table>

### A. Serious*

1 = Yes  
2 = No

Fatal, life-threatening, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, congenital anomaly/birth defect or significant medical event that may require medical or surgical intervention to prevent one or more of the other outcomes becoming serious.

### B. Grade: NCI Common Toxicity Criteria

Complete with Grades 1, 2, 3, 4 or 5

1 = Intermittent  
2 = Continuous

### C. Frequency

1 = Single Episode

### D. Action Taken - Study Drug

1 = None  
2 = Procedure or physical therapy  
3 = Blood or blood products  
4 = Withdrawn from study due to AE  
5 = Prescription drug therapy  
6 = Non-prescription drug therapy  
7 = Hospitalization  
8 = IV fluids given  
99 = Other (specify above)

### E. Action Taken - Other

1 = None  
2 = Procedure or physical therapy  
3 = Blood or blood products  
4 = Withdrawn from study due to AE  
5 = Prescription drug therapy  
6 = Non-prescription drug therapy  
7 = Hospitalization  
8 = IV fluids given  
99 = Other (specify above)

### F. Outcome

1 = Resolved  
2 = Resolved with sequelae  
3 = Death  
4 = Unknown/lost to follow-up  
5 = AE persisting  
6 = AE persisting with change in grade

### G. Relationship

1 = Related  
2 = Not Related

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Template CRF courtesy of Cellectar, Inc.
# Concomitant Medications

**CONCOMITANT MEDICATIONS**

Record below any medications, blood, blood products, or IV fluid ongoing at baseline and taken during the study. For a combination medication enter the trade name otherwise enter the generic or trade names. Provide Adverse Event number, if applicable (taken from Adverse Event CRF). Refer to the study protocol for a listing of excluded medications.

<table>
<thead>
<tr>
<th>Medication</th>
<th>Dose/Unit</th>
<th>Route (see codes below)</th>
<th>If code = 99 specify route</th>
<th>Date of Therapy</th>
<th>Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Date Started (Day/Month/Year)</td>
<td>Date Stopped (Day/Month/Year) [Enter date or check box]</td>
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*Note: Con Meds are linked to AE number*
Distinguishing AEs

- **Medical History**: Anything that started before the injection of the investigational product

- **Concomitant Illness**: Started before AE reporting window, continues during AE reporting window *unchanged*
  - *If worsens, than it is reported as an AE*

**Remember**: An AE only occurs within the AE reporting window
SCENARIO 1:

Patient has hypertension and is taking medication; start date is prior to enrollment on study; continues taking medication during study period

– **Hypertension** is *medical history*
  - Not recorded on AE CRF

– **Medication** is *concomitant medication*
  - Not recorded on AE CRF
SCENARIO 2:

Patient’s blood pressure is elevated above baseline during infusion of investigational product

– If increase in severity per protocol (or CTCAE), then **AE**
– If no increase in severity per protocol (or CTCAE), then **no AE**
– If increase in severity per protocol (or CTCAE), and related to investigational product per investigator, then **Adverse Reaction**
SCENARIO 3:

Patient’s blood pressure is elevated above baseline during follow up visit but outside of AE reporting window

– Outside of AE reporting period, not AE
  • More common with medical imaging investigational products

• The reporting period for many therapeutic studies is the entire time the patient is on study (could be many months)
  – More common for therapeutic interventions
  – Long studies have extensive AE recording
Monitoring of AEs

- Reviewing AEs is a priority for monitors

- All AEs must have source documentation (e.g. clinic note, medical record)

- It is essential to have the patient’s medical record available for review by the monitor (to make sure none are missed)

- The monitor can provide advice on completing the AE case report form properly

- When in doubt, ask your monitor or the sponsor about how to complete the AE Case Report Form

- The monitor can also connect you with the sponsor’s medical director if requested.
<table>
<thead>
<tr>
<th>Previous</th>
<th>After March 11, 2011</th>
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<tbody>
<tr>
<td>No statement about who decides if the AE is serious</td>
<td>“An adverse event or suspected adverse reaction is considered ‘serious’ if, in the view of <em>either the investigator or sponsor</em>,...</td>
</tr>
<tr>
<td>No statement about who decides if the AE is life-threatening</td>
<td>“An adverse event or suspected adverse reaction is considered “life-threatening” if, in the view of <em>either the investigator or sponsor</em>,...</td>
</tr>
</tbody>
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Guidance for Industry and Investigators; Safety Reporting Requirements for INDs and BA/BE Studies; FDA Draft Guidance September 2010
Serious Adverse Events

Previous

“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
- A congenital anomaly/birth defect”

After March 11, 2011

“An adverse event or suspected adverse reaction is considered ‘serious’ if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect”

Guidance for Industry and Investigators; Safety Reporting Requirements for INDs and BA/BE Studies; FDA Draft Guidance September 2010
Serious AEs in Medical Imaging

- Serious adverse event or serious suspected adverse reaction

- Avoid acronyms (S could be Suspected or Serious)

- All medical imaging investigators and study coordinators should be trained on proper reporting of serious AEs and serious suspected adverse reactions

- Some IRBs require reporting of all serious adverse events; some require reporting of only serious suspected adverse reactions
Example:

Your patient trips and falls down 6 steps after her research PET study and is hospitalized overnight for rib fracture and possible concussion.

- Is this a serious adverse event?
- Is this a serious adverse drug reaction?
- Is this unexpected?
  - Is there anything in the investigator brochure about hypotension, vertigo or fainting?
  - If the patient reports feeling dizzy prior to the fall, is this unexpected?
Reporting Serious AEs

• Investigator must report all serious AEs immediately upon becoming aware of the event

• Follow up information may be requested by the sponsor

• The sponsor is required to determine if the serious AE must be reported in an expedited IND safety report to the FDA and all investigators
Reporting Serious AEs

• **Sponsor** must submit an **IND safety report** if the event is:
  – A suspected adverse reaction,
  – Serious, **AND**
  – Unexpected

• Report must be filed with the FDA within **15** days of notification

• In addition, if the AE is fatal or life-threatening, a report must be filed with the FDA within **7** days of notification, with a follow up report at day 15.
Expedited Reporting Clock

15 Day Report
Unexpected Serious Adverse Reactions

7 Day Report
Unexpected Fatal or Life-Threatening Reactions

Follow up to 7 Day Report by Day 15
AEs and the IRB

- Refer to institutional IRB requirements for AE reporting

- Most IRBs require notification of serious AEs, whether or not unexpected

- All IRBs require notification of IND Safety Reports from sponsor
Resources

• **Protocol sponsor:** will have company SOPs to ensure compliance with IND regulations

• **Institutional IRB:** will have SOPs to ensure institutional compliance with IRB regulations

• **Final Safety Reporting Rule:**

• **Guidance for Industry and Investigators; Safety Reporting Requirements for INDs and BA/BE Studies; FDA Draft Guidance September 2010**

• **Journal of Clinical Research Best Practices**