Adverse Events: 
Routine Reporting and Serious Adverse Event Reporting

John Postiglione, B.S
Lorraine Rutt, B.A.
CALGB Statistical Center

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Objectives

• Define an adverse event
• Discuss terminology and grading of adverse events
• Differentiate between routine adverse events and serious adverse events
• Determine when and understand how to report adverse events
• Identify appropriate reference materials
• Successfully complete a case study using all the above information
What is an Adverse Event?

• Any unfavorable sign, symptom, or disease associated with the use of medical treatment or a procedure that may or may not be attributed to the treatment or procedure
• Adverse Events are also known as:
  – Side effects
  – Toxicities
• Abnormal lab findings that reach a criterion level may be reported as adverse events

Adverse Event Terms and Grades

• Common Toxicity Criteria (CTC) v2.0
  OR
• Common Terminology Criteria for Adverse Events (CTCAE) v3.0
• Provide:
  – Standard terminology
  – Grading criteria for adverse events
  – MedDRA codes
• Protocol dictates which version to use
Finding MedDRA Codes

- Medical Dictionary for Regulatory Activities (MedDRA)
- Common Toxicity Criteria v2.0 uses MedDRA v5.0
- Common Terminology Criteria for Adverse Events v3.0 uses MedDRA v6.0

Where to Find the CTC

- CTEP Web Site: http://ctep.cancer.gov
  - Interactive CTC Application for CTC v2.0 and v3.0
- CALGB Web Site: http://www.calgb.org
Finding the CTC and MedDRA Codes on www.calgb.org

CTCAE v 3.0 Codes

<table>
<thead>
<tr>
<th>Grade</th>
<th>Allergy/Immunology</th>
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<tbody>
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Rhinitis (including sneezing, nasal stuffiness, postnasal drip) 10039087
Supra-Ordinate Terms

- Used in CTCAE v3.0 only.
- Grouping of terms based on disease process, signs, symptoms, or diagnosis.
- Followed by “Select” and a list of specific AE terms related to supraordinate item.

Example of Supra-Ordinate Term
Two Types of Adverse Event Reporting

• Routine reporting
  – All adverse event forms per protocol
• Expedited reporting for serious events
  – Submit adverse event forms per protocol
  – Expedited reporting through AdEERS

Reporting Routine Adverse Events

Complete Adverse Event Forms and Supporting Documentation
(C-260 Remarks Addenda, etc.)
Per Protocol Schedule

Submit to CALGB Statistical Center,
Data Operations
Durham, NC
Completing an AE Form

- Expected Adverse Events
- Match MedDRA code and event name
- Determine grade for all events
  - If event is not present, grade = 0
  - If event is not assessed, grade = -1
- Provide attribution code

Completing the Adverse Event Form

Other Events
- Supply the MedDRA code and event term from the CTC.
- Determine the grade
- Provide attribution code
Coding Supra-Ordinate Terms

On the right side of the form provide:

- MedDRA code for the selected site.
- Event term including the selected site.
- Grade (0-5)
- Attribution

Grading Adverse Events

- All reportable adverse events must be graded using the correct reference.
- There can be only one grade 5 event.
- If adverse event happens more than once during a reporting period, report the grade associated with most severe event.
- Continue reporting an adverse event until it resolves.
Grading Adverse Events

- For some events, certain grades are not defined, and therefore are not allowed.
- Do not modify grade based on a patient’s baseline condition.
- If condition does not worsen, grade = -1
- Use the correct version of CTC.

Adverse Event Attribution Codes

1 = Unrelated to treatment
2 = Unlikely related to treatment
3 = Possibly related to treatment
4 = Probably related to treatment
5 = Definitely related to treatment
Secondary Malignancies

- Secondary malignancy is due to treatment for a previous cancer.
- Report all secondary malignancies.
  - Routine adverse event reporting via study-specific adverse event forms or follow-up forms
  - Use C-1001 New Malignancy Form
  - Use NCI AML/MDS Form for Secondary AML/MDS

New Primary Cancers

- New primary cancer (a.k.a. second malignancy)
  - a new malignancy not associated with treatment for a previous cancer
- Report
  - Use the C-1001 New Malignancy Form for new primary cancers
  **and/or**
  - Use the study specify follow up form
Adverse Event Expedited Reports (AdEERS)

AdEERS = Adverse Event Expedited Reporting System

- Should I report?
- When to report?
- How to report?
- Where to report?
Adverse Event
Expedited Reports (AdEERS)

- Consider these questions when deciding whether to report:
  - Is an investigational or commercial agent involved?
  - Is it a Phase I, II, or III trial?
  - What is the grade of severity?
  - Was there a hospitalization or death within 30 days of treatment?
  - Is event expected or unexpected?
  - Is agent suspected of causing event (attribution)?

AdEERS Protocol-Specific Guidelines

<table>
<thead>
<tr>
<th>Grade</th>
<th>Grades 4 &amp; 5*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
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<tr>
<td>Grade 2</td>
<td></td>
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<tr>
<td>Grade 3</td>
<td></td>
</tr>
<tr>
<td>Grade 4 &amp; 5*</td>
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</table>

Unrelated
Unlikely
Possible
Definite

Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND or non-CTEP IND require reporting as follows:
- AdEERS 24-hour notification followed by complete report within 5 calendar days for:
  - Grade 4 and Grade 5 unexpected events
  - AdEERS 10 calendar day report:
    - Grade 3 unexpected events with hospitalization or prolongation of hospitalization
    - Grade 4-5 expected events

* Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

March 2005
When and How to Report AdEERS

- **When?**
  - Within 24 hours; 5 Calendar Days
  - Within 10 calendar days of learning of the event
- **How?**
  - Electronic AdEERS
  - At the CTEP Website: [http://ctep.cancer.gov](http://ctep.cancer.gov)
  - CALGB Adverse Event Form
- Remember to send supporting documentation to the NCI, the CALGB Central Office, and the CALGB Statistical Center, Data Operations.

Where to Report AdEERS

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Institution
  NCI/CTEP
    CALGB Central Office (Chicago, IL)
  Local IRB

Study Chair

CALGB Statistical Center, Data Operations (Durham, NC)
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AdEERS Help

• Policy-related, medical questions and administrative issues, contact:
  – AdEERS MD Help Desk: 301-897-7497
  – AdEERS MD E-mail: AdEERSMD@TECH-RES.COM

• Technical and training issues, contact:
  – NCI CTEP Help Desk: 301-840-8202
  – NCI CTEP E-mail: ncictephelp@ctep.nci.nih.gov

Routine vs. Expedited Reporting

Routine Reporting
• Adverse Event Forms
  – At regular intervals, per protocol

Expedited Reporting
• AdEERS
  – As defined by the protocol, within 5 days
  – Submit to your local IRB

• Adverse Event Forms
  – At regular intervals, per protocol
Review

• Check the protocol for the correct version of the CTC.
• Use the CTC to determine the event name, grade, and MedDRA code.
• Submit routine Adverse Event Forms per protocol.
• Check the protocol or CALGB web site for which events must be submitted via AdEERS.

Resources

• Protocol
• http://ctep.cancer.gov
• www.calgb.org
• AdEERS/CTEP Help Desks
• CALGB Central Office contact
  – Linda Bressler, Pharm. D. (CALGB Director of Regulatory Affairs)
    • E-mail: bressler@uic.edu
    • Phone: 773-834-7975
Please proceed to:

**Disease Response**

*Location: Salons F/G/H*
Please proceed to:

**LUNCH**

*Location: Salon E*

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Please proceed to:

**Look at Me**

*Location: Salons A/B/C/D*