



Adverse Events

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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

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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

How Do We Describe Adverse Events?

- Terminology Provided by the NCI
 - Common Toxicity Criteria (CTC) v2.0
 - Common Terminology Criteria for Adverse Events (CTCAE) v3.0
- Protocol specifies the correct version
- Provides:
 - Standard terminology
 - Grading criteria for adverse events
 - MedDRA codes

MedDRA Codes

- Medical Dictionary for Regulatory Activities (MedDRA)
 - Provides a numeric code for every adverse event
 - Paired with the CTC
- CTC v2.0 uses MedDRA v5.0
- CTCAE v3.0 uses MedDRA v6.0

Where to Find the CTC

CALGB Web Site:
<http://www.calgb.org>

Finding the CTC and MedDRA Codes on www.calgb.org

The screenshot shows the CALGB website interface in Microsoft Internet Explorer. The address bar displays http://www.calgb.org/Private/COOP_Groups/CALGB/studies/studies.php. The navigation menu includes Home, Member Site, Studies, Patient Registration, LabTrak, Reports, Directory, Meetings, Resources, and Policies. The main content area is titled 'Protocols' and contains several sections: Active Protocols, Closed Protocols, Intergroup Access, Monthly Protocol Postings, and Protocols in Development. A 'Forms' section is highlighted with a red arrow, containing 'Study Specific Forms for Active Studies' and 'Study Specific Forms for Closed Studies'. The 'Study Specific Forms for Closed Studies' link is also highlighted with a red arrow. The left sidebar includes 'CALGB Web Search', 'CALGB Site Navigation', 'Web Site Help', and 'Quick Links'. The right sidebar contains 'Studies FAQs', 'Past Postings', and 'Recent Study Postings'.

CTCAE v3.0 Codes

ALLERGY/IMMUNOLOGY						
Page 1 of 1						
Adverse Event	Short Name/MedDRA	Grade				
		1	2	3	4	5
Allergic reaction/hypersensitivity (including drug fever)	Allergic reaction 10020755	Transient flushing or rash; drug fever <38°C (<100.4°F)	Rash; flushing; urticaria; dyspnea; drug fever ≥38°C (≥100.4°F)	Symptomatic bronchospasm, with or without urticaria; parenteral medication(s) indicated; allergy-related edema/angioedema; hypotension	Anaphylaxis	Death
REMARK: Urticaria with manifestations of allergic or hypersensitivity reaction is graded as Allergic reaction/hypersensitivity (including drug fever). ALSO CONSIDER: Cytokine release syndrome/acute infusion reaction.						
Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip)	Rhinitis 10039087	Mild, intervention not indicated	Moderate, intervention indicated	—	—	—
REMARK: Rhinitis associated with obstruction or stenosis is graded as Obstruction/stenosis of airway – Select in the PULMONARY/UPPER RESPIRATORY CATEGORY.						
Autoimmune reaction	Autoimmune reaction 10003815	Asymptomatic and serologic or other evidence of autoimmune reaction, with normal organ function and intervention not indicated	Evidence of autoimmune reaction involving a non-essential organ or function (e.g., hypothyroidism)	Reversible autoimmune reaction involving function of a major organ or other adverse event (e.g., transient colitis or anemia)	Autoimmune reaction with life-threatening consequences	Death
ALSO CONSIDER: Colitis; Hemoglobin; Hemolysis (e.g., immune hemolytic anemia, drug-related hemolysis); Thyroid function, low (hypothyroidism).						
Serum sickness	Serum sickness 10040400	—	—	Present	—	Death
NAVIGATION NOTE: Splenic function is graded in the BLOOD/BONE MARROW CATEGORY.						
NAVIGATION NOTE: Urticaria as an isolated symptom is graded as Urticaria (hives, welts, wheals) in the DERMATOLOGY/SKIN CATEGORY.						
Vasculitis	Vasculitis 10047128	Mild, intervention not indicated	Symptomatic, non-steroidal medical intervention indicated	Steroids indicated	Ischemic changes; amputation indicated	Death

Supra-Ordinate Terms

- Also referred to as select-site events
- Listing of specific sites for certain events
- Allows for increased specificity
- Not used in version 2

Example of Supra-Ordinate Term

#1 (GRADE 3 OR 4)		INFECTION - SELECT					Page 1 of 3
Adverse Event	Short Name/MeDRA	Grade					
		1	2	3	4	5	
AUDITORY/EAR		GENERAL		PULMONARY/UPPER RESPIRATORY			
- External ear (otitis externa) - 90030192		- Catheter-related - 90030174		- Bronchus - 90030172			
- Middle ear (otitis media) - 90030228		- Foreign body (e.g., graft, implant, - 90030212		- Larynx - 90030212			
CARDIOVASCULAR		RENAL/GENITOURINARY			20		
- Artery - 90030160		- Bladder (urinary) - 90030164			224		
- Heart (endocarditis) - 90030166		- Kidney - 90030210			158		
- Spleen - 90030278		- Prostate - 90030260			90030286		
- Vein - 90030300		- Ureter - 90030290			288		
DERMATOLOGY/SKIN		- Urethra - 90030292			94		
- Lip/perioral - 90030216		- Urinary tract NOS - 90030294			2710N		
- Perioral - 90030252							
- Skin (cellulitis) - 90030271							
- Ungual (nails) - 90030284							
GASTROINTESTINAL							
- Abdomen NOS - 90030111							
- Anal/perianal - 90030156							
- Appendix - 90030166							
- Cecum - 90030176							
- Colon - 90030180							
- Dental-tooth - 90030186							
- Duodenum - 90030188							
- Esophagus - 90030190							
- Ileum - 90030204							
- Jejunum - 90030208							
- Oral cavity-gums (gingivitis) - 90030242							
- Peritoneal cavity - 90030254							
- Rectum - 90030262							
- Salivary gland - 90030264							
- Small bowel NOS - 90030272							
- Stomach - 90030280							
		nerve-peripheral - 90030220		- Pelvis NOS - 90030146			
		- Spinal cord (myelitis) - 90030278		- Penis - 90030250			
		OCULAR		- Scrotum - 90030286			
		- Conjunctiva - 90030162		- Uterus - 90030296			
		- Cornea - 90030184		- Vagina - 90030288			
		- Eye NOS - 90030194		- Vulva - 90030302			
		- Lens - 90030214					

Two Types of Adverse Event Reporting

- Routine reporting
 - Follow data submission schedule
 - Only require the CALGB AE Form
- Expedited reporting for serious events
 - Submit CALGB AE form per protocol
 - Expedited reporting through AdEERS

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Reporting Routine Adverse Events

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



Submit to CALGB Statistical Center,
Data Operations
Durham, NC



Routine Adverse Event Reports

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

MedDRA code ¹	CTC adverse event term	CTC AE ² grade ¹	CTC AE ² Attribution Code ³
10029363	Neutrophils/granulocytes	<input type="checkbox"/>	<input type="checkbox"/>
10035528	Platelets	<input type="checkbox"/>	<input type="checkbox"/>
10018876	Hemoglobin	<input type="checkbox"/>	<input type="checkbox"/>
10016288	Febrile neutropenia	<input type="checkbox"/>	<input type="checkbox"/>
10021099	Hypotension	<input type="checkbox"/>	<input type="checkbox"/>
10005364	Bilirubin	<input type="checkbox"/>	<input type="checkbox"/>
10012457	Rash/desquamation	<input type="checkbox"/>	<input type="checkbox"/>
10030220	Esophagitis	<input type="checkbox"/>	<input type="checkbox"/>
10012745	Diarrhea	<input type="checkbox"/>	<input type="checkbox"/>
10028813	Nausea	<input type="checkbox"/>	<input type="checkbox"/>
10047706	Vomiting	<input type="checkbox"/>	<input type="checkbox"/>
10037063	INR	<input type="checkbox"/>	<input type="checkbox"/>
10000636	PTT	<input type="checkbox"/>	<input type="checkbox"/>
10024119	Left ventricular systolic dysfunction	<input type="checkbox"/>	<input type="checkbox"/>

** Infection with grade 3 or 4 neutrophils } →

Grading Adverse Events

- Use the correct version of the CTC
- There can be only one grade 5 event
- Report the most severe grade
- Continue reporting an adverse event until it resolves

Grading Adverse Events

- Some events do not have 5 grades
 - Represented as a dash (-) in the CTC
- Baseline conditions are not reported unless they worsen
- If an expected baseline event does not worsen then grade = -1

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

Cancer as an Adverse Event

- Secondary Malignancy
 - Due to treatment for a previous cancer
- New Primary Cancer
 - Not associated with treatment

Reporting Secondary Malignancies

- Reported on several forms
 - Study specific adverse event form
 - Some follow-up forms
 - CALGB: New Malignancy Form (C-1001)
 - NCI AML/MDS Form

Reporting New Primary Cancers

- Study specific reporting
 - CALGB: New Malignancy Form (C-1001)
 - 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?

Should I Use AdEERS?

- Things to know:
 - Investigational or commercial agent
 - Phase of trial
 - Severity of event
 - Hospitalization
 - Is event expected or unexpected
 - Relation to treatment

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AdEERS Protocol-Specific Guidelines

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5 ²	Grades 4 & 5 ²
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	without Hospitalization	Expected with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hrs; 5 Calendar Days	10 Calendar Days

¹ 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 5 expected events

² 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

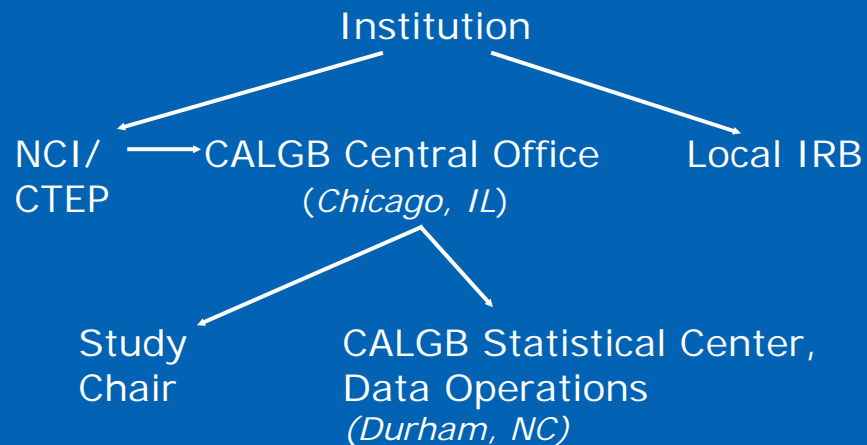
- When?
 - Within 24 hours; 5 calendar days
 - Within 10 calendar days of learning of the event
- How?
 - At the CTEP website: <http://ctep.cancer.gov>
 - CALGB Adverse Event Form
- Remember to send supporting documentation to the NCI, the CALGB Central Office, and the CALGB Statistical Center, Data Operations.

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AdEERS **does not**
replace the
protocol-specific
Adverse Event Form

Where to Report AdEERS



AdEERS Help

- Policy-related, medical questions and administrative issues, contact:
 - AdEERS MD Help Desk: (301) 897-7497
 - AdEERS MD Email: AdEERSMD@TECH-RES.COM
- Technical and training issues, contact:
 - NCI CTEP Help Desk: (301) 840-8202
 - NCI CTEP Email: ncictephhelp@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 Data Submission Schedule 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
 - AdEERS MD Help Desk: (301) 897-7497
 - NCI CTEP Help Desk: (301) 840-8202
- AdEERS Computer Based Training:
http://ctep.cancer.gov/reporting/AdEERS_CBT_v3/welcome.html
- CALGB Central Office contact
 - Linda Bressler, Pharm. D. (CALGB Director of Regulatory Affairs)
 - Email: bressler@uic.edu
 - Phone: (773) 834-7973

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