

# **CTEP NCI Adverse Event Reporting Guidelines**

# Adverse Event

## *(21CFR312, ICH GCP, OHRP Guidance)*

- Any unfavorable or unintended:
  - Sign, including abnormal laboratory findings
  - SymptomOR
  - Disease
    - having been absent at baseline, or, if present at baseline, appears to worsen
- Temporal association with a medical treatment or procedure
- **Regardless of attribution** (relationship of event to medical treatment or procedure)

# Severity

- Assessing the severity is done by using a standard language/dictionary called the Common Terminology Criteria for Adverse Events (CTCAE v.3.0)
- CTCAE provides a uniform method of grading adverse events without regard to timing or cause of the events
- Events are graded on a severity scale of 1-5
  - 1 = Mild
  - 2 = Moderate
  - 3 = Severe
  - 4 = Life-threatening
  - 5 = Fatal

# Routine Reporting

- What data is reported and frequency of data reporting dependent on monitoring method
  - CTMS: Q 2 weeks
  - CDUS: Quartely

# Routine CTMS AE Reporting

## 3.1.2 Clinical Trials Monitoring System (CTMS)

The CTMS is the non-Governmental organization contracted by CTEP to receive, review and perform data management tasks on individual patient case report forms for Phase 1 investigational agent studies designated for CTMS data reporting.

Table B: CTMS Guidelines for Routine Adverse Event Reporting for Trials using Agent(s) under a CTEP IND

Attribution	Adverse Event				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	CTMS	CTMS	CTMS	CTMS	CTMS
Unlikely	CTMS	CTMS	CTMS	CTMS	CTMS
Possible	CTMS	CTMS	CTMS	CTMS	CTMS
Probable	CTMS	CTMS	CTMS	CTMS	CTMS
Definite	CTMS	CTMS	CTMS	CTMS	CTMS

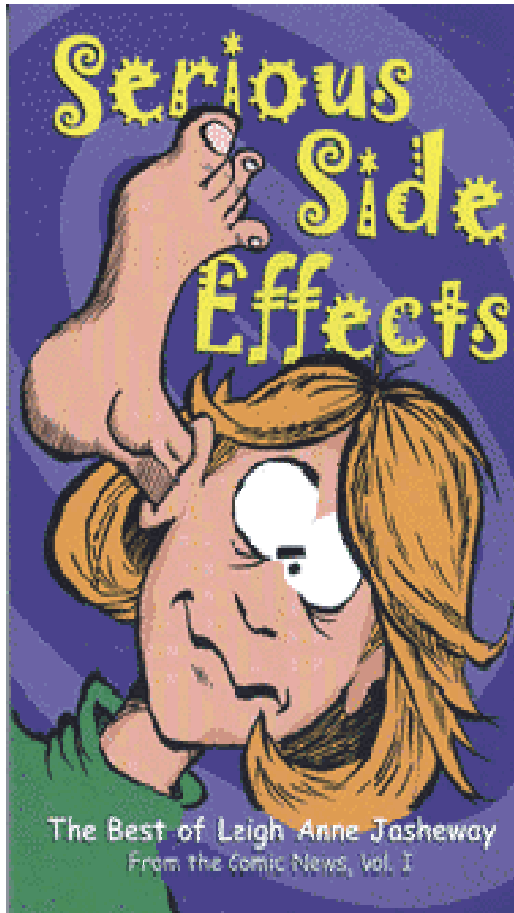
# Routine CDUS AE Reporting

## 3.1.1 Clinical Data Update System (CDUS)

The CDUS is the primary repository of clinical data for CTEP, NCI.

Table A: CDUS Guidelines for Routine Adverse Event Reporting on Trials using Agent(s) under a CTEP IND

Attribution	Adverse Event				
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			CDUS	CDUS	CDUS
Unlikely			CDUS	CDUS	CDUS
Possible	CDUS	CDUS	CDUS	CDUS	CDUS
Probable	CDUS	CDUS	CDUS	CDUS	CDUS
Definite	CDUS	CDUS	CDUS	CDUS	CDUS



# EXPEDITED ADVERSE EVENT REPORTING

# Expedited Adverse Events

- Subset of adverse events that are reported to regulatory/oversight groups (i.e.: IRB, Sponsor, FDA, OBA) in an expedited manner
  - based on severity, expectedness, and seriousness
- Often referred to by many aliases including:
  - Serious Adverse Event
  - Serious Adverse Experience
  - Expedited Adverse Event
  - Adverse Drug Reaction



# **Serious Adverse Event (SAE)** ***(21 CFR 312, ICH GCP, OHRP Guidance)....***

Any adverse event occurring at any dose that results in any of the following outcomes:

- Death
- Life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity

OR

- Congenital anomaly/birth defect

# **...Serious Adverse Event (SAE)** ***(21 CFR 312, ICH GCP, OHRP Guidance)***

Important medical events that may not result:

- in death,
- be life-threatening,
- or require hospitalization

may be considered a serious adverse drug experience when, they may:

- jeopardize the patient/subject  
AND
- may require medical or surgical intervention to prevent one of the outcomes above

# Unexpected Adverse Drug Experience

## **21 CFR 312 & ICH GCP:**

Any adverse experience that is not listed in the current labeling for the drug or product (Package Insert/Investigator's Brochure)

## **OHRP Guidance:**

Any adverse event that is not described in the protocol, consent, current labeling for the drug or product

# CTEP Reporting Guidelines

- Contains information on reporting adverse events that are both routine and expedited
- Current version: December 15, 2004  
(effective January 1, 2005)
- Protocol specific guidelines supersede CTEP Guidelines

# CTEP Definition - Unexpected

Any adverse event (AE) which is **NOT** listed in the *Comprehensive Adverse Events and Potential Risks (CAEPR)* list, formerly the *Agent Specific Adverse Event List (ASAEL)*.

# CAEPR

- Complete list of potentially related AEs associate with an agent under a CTEP IND
- Source:
  - AdEERS
  - IB
  - Package inserts
  - Literature (e.g., abstracts, publications)
- Distributed to every Investigator with an approved LOI or active CTEP protocol (includes updates)
- Updates may or may not require protocol amendment
- Inquires: [AdEERSMD@tech-res.com](mailto:AdEERSMD@tech-res.com)

# CAEPR Sample #1

## Comprehensive Adverse Events and Potential Risks List (CAEPR) for Agent X (NSC XXXXXX)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold** and *italicized* text. This subset of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' <http://ctep.cancer.gov/reporting/adeers.html> for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information. Below is the CAEPR for Agent X.

No frequency  
data provided

Version 1.5<sup>1</sup>

Category (Body System)	Adverse Events with Possible Relationship to Agent X (CTCAE v3.0 Term)	'Agent Specific Adverse Event List' (ASAEL)
BLOOD/BONE MARROW		
	Platelets	<b><i>Platelets</i></b>
CARDIAC ARRHYTHMIA		
	AV block-first degree	
CARDIAC GENERAL		
	Hypotension	
PULMONARY/UPPER RESPIRATORY		
	Cough	
	Dyspnea	

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [ADEERSMD@tech-res.com](mailto:ADEERSMD@tech-res.com). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

Also reported on Agent X trials but with the relationship to Agent X still undetermined:

**BLOOD/BONE MARROW** - hemoglobin  
**CONSTITUTIONAL SYMPTOMS** - fatigue/hypoactivity  
**PAIN** - muscle pain

**Animal Data:** The following toxicities have been observed in animal studies with 17-DMAG: bone dysplasia; bone hyperplasia; bone marrow inflammation; bone marrow necrosis; decreased reticulocytes; hemoglobin; leukocytes; lymphopenia; neutropenia; platelets; increased fibrinogen; fatigue/hypoactivity; weight loss; injection site reaction.

**Note:** Agent X in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

# CAEPR Sample #2

## Comprehensive Adverse Events and Potential Risks List (CAEPR) for Agent X (NSC XXXXXX)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a **subset**, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with **bold and italicized** text. This **subset** of AEs (ASAEL) contains events that are considered 'expected' for expedited reporting purposes only. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' <http://ctep.cancer.gov/reporting/adeers.html> for further clarification. Frequency is provided based on 50 patients. Below is the CAEPR for Agent X.

Frequency  
data provided

Version 2.3, September 1, 2006<sup>1</sup>

Adverse Events with Possible Relationship to Agent X (CTCAE v3.0 Term) [n=50 patients]			'Agent Specific Adverse Event List' (ASAEL)
Likely (>20%)	Less Likely (<20%)	Rare but Serious (<3%)	
BLOOD/BONE MARROW			
	Hemoglobin		<i>Hemoglobin</i>
	Leukocytes (total WBC)		
CARDIAC GENERAL			
	Hypotension		
DEATH			
		Death not associated with CTCAE term: Sudden death	
PAIN			
	Pain - muscle		<i>Pain - muscle</i>
PULMONARY/UPPER RESPIRATORY			
	Cough		
	Dyspnea		

<sup>1</sup>This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting [ADEERSMD@tech-res.com](mailto:ADEERSMD@tech-res.com). Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

**Also reported on Agent X trials but with the relationship to Agent X still undetermined:**

**ALLERGY/IMMUNOLOGY** - allergic reaction

**GASTROINTESTINAL** - dry mouth; mucositis/stomatitis; taste alteration

**OCULAR/VISUAL** - blurred vision

**Animal Data:** The following toxicities have been observed in animal studies with Agent X:  
possible renal dysfunction

**Note:** Agent X in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.



# AdEERS

- Web-based reporting system
- Used for all protocols utilizing agents under a CTEP IND
- Must be used for all Cooperative Group protocols (commercial agent, radiation, surgery, device, and combinations)
- <http://ctep.cancer.gov/reporting/adeers.html>

# 24-hour Notification

- Early detection system for potential problems on CTEP sponsored studies
- Allows CTEP to be compliant with the regulations
- Preliminary Report that **Does NOT** replace the full AdEERS report
- Within 24-hours of learning of the event
- Refer to protocol for requirements
- AdEERS abbreviated report:
  - Reporter info
  - Patient info
  - AE
  - Note: All other sections of report are available and may be completed at the time of the “24-hour Notification”

# Expedited Reporting Guidelines

## Phase 1

### 3.4.1 Phase 1 Trials utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent

Table C: Reporting Requirements for Adverse Events that occur within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent on Phase 1 Trials

	1	2	2	3		3		4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected with Hospitalization	Unexpected without Hospitalization	Expected with Hospitalization	Expected without Hospitalization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour, 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour, 5 Calendar Days	24-Hour, 5 Calendar Days	10 Calendar Days	Not Required	24-Hour, 5 Calendar Days

<sup>1</sup>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 require reporting as follows:

AdEERS 24-hour notification followed by complete report within 5 calendar days for:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected and unexpected events

<sup>2</sup>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.

December 15, 2004

# Expedited Reporting Guidelines

## Phase 2 and 3

### 3.4.2 Phase 2 and Phase 3 Trials utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events that occur within 30 Days of the Last Dose of the Investigational Agent

Table D: Reporting Requirements for Adverse Events that occur within 30 Days<sup>1</sup> of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

	1	2	2	3		3		4 & 5	4 & 5 <sup>2</sup>
	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected	Expected
				with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization		
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-Hour, 5 Calendar Days	10 Calendar Days

<sup>1</sup>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 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

<sup>2</sup>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.

# AdEERS Processing

