CTEP, NCI GUIDELINES: ADVERSE EVENT REPORTING REQUIREMENTS

Effective January 1, 2005

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RECORD OF CHANGES

Update Date	Brief Description
12/15/04	Initial Document Creation
12/29/04	Minor editorial revisions include removing the word *'Expedited'* from the document's title and adding the NCI CTEP Help Desk toll-free phone number.
1/3/05	PDF conversion process correction to provide legible process flow in Attachment A (pg 15).
1/17/05	Corrected date in Record of Changes. Replaced Attachment A illustration for accurate PDF conversion.
6/30/06	Revised the cover date to read 'Effective January 1, 2005'.

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Tables

1 INTRODUCTION

The Federal Food and Drug Administration (FDA), HHS, defines in the Code of Federal Regulations (CFR) procedures and requirements governing the use of investigational new drugs and the monitoring of serious adverse events (21 CFR 312). The Cancer Therapy Evaluation Program (CTEP), NCI, sponsors an extensive national program of cancer research as both an Investigational New Drug application (IND) sponsor and/or a funding sponsor and is responsible for ensuring that the research is conducted in accordance with Federal Regulations.

1.1 Purpose

The purpose of this document from CTEP, NCI, as an IND sponsor, is to:

1. Provide guidelines for investigators regarding adverse event (AE) reporting to CTEP for agents under a CTEP IND;
2. Ensure that investigators submit sufficient information to allow CTEP, Investigational Drug Branch (IDB) physicians adequate information to make an independent assessment of AEs that occur on trials utilizing an agent under a CTEP, IND; and
3. Determine if an expedited report to the FDA is warranted and if so, submit the report within the timeframe stipulated in the CFR.

A second purpose of this document is to explain the expanded use of AdEERS for expedited AE reporting for Cooperative Group trials utilizing commercial agents. All Cooperative Groups must use AdEERS for:

1. Trials utilizing a commercial agent only;
2. Trials utilizing an investigational agent under a CTEP IND and a commercial agent on separate arms;
3. Trials utilizing an investigational agent under a CTEP IND and a commercial agent on the same arm.

1.2 Investigator Responsibility - Adverse Event Documentation and Reporting

Clinical investigators and ultimately the protocol Principal Investigator (PI) have the primary responsibility for AE identification, documentation, grading, and assignment of attribution. The CTEP, NCI Common Toxicity Criteria v2.0 (CTC) and Common Terminology Criteria for Adverse Events v3.0 (CTCAE) are designed as instruments to be used to document AEs identified through a combination of clinical and laboratory evaluation. CTC/CTCAE are not tools to assist with data extraction from source documents without the direct participation and supervision of clinical investigators. AE grading and assignment of attribution require documentation by medical personnel who are directly involved in the clinical care of protocol subjects.

The CTEP, NCI adverse event reporting requirements and timing of expedited reports include established criteria based upon:

Phase of trial

AE as listed in CTC/CTCAE

Unexpected/expected as determined by the CTEP Agent Specific Adverse Event List (ASAEL)

Attribution

Protocol specific requirements

AE collection and reporting is a routine part of every clinical trial. For protocols utilizing an agent under a CTEP IND, this is the process for investigators:

1. Identify the event using the CTC/CTCAE criteria;
2. Determine if the AE is unexpected or expected (refer to the ASAEL and/or protocol);
3. Assign grade of the event using the CTC/CTCAE criteria;
4. Determine attribution (i.e., if the AE is related to the medical intervention).
5. Identify whether the AE requires expedited reporting to CTEP via the Adverse Event Expedited Reporting System (AdEERS). Investigators must use information regarding the AE, expected/unexpected, grade, and attribution along with the AE reporting section in each protocol to initiate an AdEERS report.
    - CTEP defines routine AE reporting requirements for Phase 1 and Phase 2 trials as described in Table A and Table B.

Important: All AEs reported via AdEERS must also be reported via the routine reporting requirements defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators.

1.2.1 Distribution of Expedited Reports for Agents under a CTEP IND

An expedited AE report associated with an agent under a CTEP IND requires electronic submission to CTEP via AdEERS. Reports must be submitted within the timeframes specified in Table C and Table D. A copy of all expedited reports must be sent to the local Institutional Review Board (IRB) according to local IRB policies and procedures.

1.2.2 Distribution of Expedited Reports for non-CTEP IND Agents

AdEERS is programmed to send commercial agent expedited reports submitted by Cooperative Groups directly to the FDA. Refer to each protocol for specific AE reporting requirements or exceptions. CTEP does not review commercial agent or non-CTEP IND expedited reports.

2 DEFINITIONS

2.1 Adverse Event (AE)

Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of unrelated, unlikely, possible, probable, or definite). Each AE is a unique representation of a specific event used for medical documentation and scientific analysis.

2.2 Toxicity

The historical use of the term 'toxicity,' while not clearly defined by regulatory organizations, has been described as an AE that has a causal relationship to investigational treatment. The CTEP, NCI CTCAE v3.0 reflects the change away from the use of the term 'toxicity.'

2.3 Serious Adverse Event (SAE)

An SAE is defined in the FDA CFR 312 as 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, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Serious AEs are defined by FDA and therefore seriousness (not severity) serves as a guide for defining regulatory reporting obligations for patient/subject safety. '**Serious**' is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. FDA Federal Regulations require IND sponsors to report serious AEs via expedited reporting.

2.4 Severity

'Severity' is not the same as 'serious.' Serious is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. The term 'severe' is often used to describe the intensity (severity) of a specific event (as in mild, moderate, severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). Seriousness (not severity) serves as a guide for defining regulatory reporting obligations. Most AEs in CTC/CTCAE include clinical criteria that describe patient/event outcomes or indicated interventions to more clearly substantiate seriousness.

2.5 Life-Threatening Adverse Event

Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

2.6 Common Toxicity Criteria Version 2.0 (CTC) and Common Terminology Criteria for Adverse Events V3.0 (CTCAE)

The CTC v2.0, published in 1998, continues to be used for legacy protocols. The current version is the Common Terminology Criteria for Adverse Events (CTCAE v3.0), and reflects the change away from the use of 'toxicity.' Both CTC v2.0 and CTCAE v3.0 provide a descriptive terminology that is to be utilized for AE reporting. Each AE is a unique representation of a specific event used for medical documentation and scientific analysis. A grading scale is provided for each AE term.

2.7 Grade

CTC/CTCAE are the foundation of the CTEP, NCI Guidelines: Adverse Event Reporting Requirements for CTEP, NCI Investigational Agents. Grade is an essential element of the Guidelines and, in general, relates to seriousness for the purposes of regulatory reporting to CTEP as follows:

Grade	Description
0	No AE or within normal limits
1	Mild AE (minor; no specific medical intervention; asymptomatic laboratory findings only, radiographic findings only; marginal clinical relevance)
2	Moderate AE (minimal intervention; local intervention; noninvasive intervention [packing, cautery])
3	Severe and undesirable AE (significant symptoms requiring hospitalization or invasive intervention; transfusion; elective interventional radiological procedure; therapeutic endoscopy or operation)
4	Life-threatening or disabling AE (complicated by acute, life-threatening metabolic or cardiovascular complications such as circulatory failure, hemorrhage, sepsis. Life-threatening physiologic consequences; need for intensive care or emergent invasive procedure; emergent interventional radiological procedure, therapeutic endoscopy or operation)
5	Fatal AE

2.8 Unexpected/Expected Adverse Events

2.8.1 Comprehensive Adverse Event and Potential Risks (CAEPR)

Introduced in August 2004, the CAEPR is a complete list of reported and/or potential AEs associated with an agent under a CTEP IND. The CAEPR combines information previously maintained in two separate documents:

1. AdEERS Agent Specific Adverse Event List (ASAEL)
2. AEs listed in the pharmaceutical data sheet labeled 'Reported Adverse Events and Potential Risks.'

2.8.2 Agent Specific Adverse Event List (ASAEL)

The ASAEL is a subset of AEs within the CAEPR. This subset contains events that are considered expected for expedited reporting requirements only. As the ASAEL is updated, the revised versions are sent to all Principal Investigators registered to protocols using the agent. A current version of the ASAEL may also be obtained via e-mail from AdEERSMD@tech-res.com.

2.8.3 Expected Adverse Event (for Expedited Reporting Purposes for Agents under a CTEP IND)

'Expected' AEs for expedited reporting purposes only are listed in the ASAEL (a subset of the CAEPR).

2.8.4 Expected Adverse Event (for Expedited Reporting Purposes for non-CTEP IND Agents)

The determination of whether an AE is expected for commercial agents is based on available sources including the package insert and/or the Investigator's Brochure. AdEERS is not programmed to guide the reporter about expectedness for commercial agents.

2.8.5 Unexpected Adverse Event (for Expedited Reporting Purposes for Agents under a CTEP IND)

'Unexpected' AEs are those not listed in the ASAEL.

2.8.6 Unexpected Adverse Event (for Expedited Reporting Purposes for non-CTEP IND Agents)

Unexpected AEs for commercial agents are those not listed on available sources including the package insert, the Investigator's Brochure, or the protocol.

2.9 Attribution

The determination of whether an AE is related to medical treatment or procedure.

CTC/CTCAE do not define an AE as necessarily 'caused by a therapeutic intervention.' The clinical investigator must assign attribution for an adverse event after naming and grading of the event.

Adverse Event Attribution Categories:

Attribution	Description
Unrelated	The AE *is clearly NOT related* to the intervention
Unlikely	The AE *is doubtfully related* to the intervention
Possible	The AE *may be related* to the intervention
Probable	The AE *is likely related* to the intervention
Definite	The AE *is clearly related* to the intervention

2.10 Commercial Agent

A commercial agent is one approved by the FDA for commercial distribution. A commercial agent may also be used as an investigational agent (under an IND). Refer to the protocol document to determine if an agent is being used as an investigational or commercial agent for the protocol. In general, only Grade 4 and 5 events that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.

2.11 Investigational Agent

An investigational agent is one being studied under an Investigational New Drug Application (IND). In some instances, a commercial agent may also be considered investigational when used under an IND.

2.12 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm. A secondary malignancy is unrelated to the first cancer that was treated, and may occur months or even years after initial treatment.

Any malignancy possibly related to cancer treatment (including AML/MDS) is reported via the routine reporting mechanisms outlined in each protocol.

Important: Secondary Malignancy is an exception to CTEP, NCI Adverse Event Reporting Guidelines.

- CTC v2.0 describes Secondary Malignancy "Grade 4, present," but CTEP, NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy.
- CTCAE v3.0 describes Secondary Malignancy –possibly related to cancer treatment (Specify, ___) Grade 3 "Non-life-threatening basal or squamous cell carcinoma of the skin; Grade 4 "solid tumor, leukemia or lymphoma." CTEP, NCI does not require AdEERS Expedited Reporting for any (related or unrelated to treatment) Secondary Malignancy.
- A diagnosis of AML/MDS following treatment with an agent under a CTEP IND is to be reported using the form available from the CTEP Web site at http://ctep.cancer.gov and faxed to CTEP at 301-230-0159.

2.13 Second Cancer

A second cancer is a new primary cancer in a person with a history of another cancer.

3 CTEP, NCI ADVERSE EVENT REPORTING GUIDELINES

3.1 Routine Adverse Event Reporting

All AEs must be reported using the routine reporting requirements described in Table A and Table B. In general, CTEP defines routine AE reporting guidelines for Phase 1 and Phase 2 trials. Refer to the CDUS website http://ctep.cancer.gov for Phase 3 routine AE reporting requirements.

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

	Adverse Event				
Attribution	**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

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

	Adverse Event				
Attribution	**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

3.2 Expedited Adverse Event Reporting

3.2.1 Adverse Event Expedited Reporting System (AdEERS)

CTEP's original web-based system for electronic submission of expedited reports on protocols utilizing a CTEP sponsored IND was published in 1998. The current version of AdEERS provides pathways for all Cooperative Group protocols including commercial agent-only; radiation-only; surgery-only; device-only; all combinations. An expedited AE report for all protocols utilizing agents under a CTEP IND must be submitted electronically to CTEP via AdEERS.

In the rare event when Internet connectivity is disrupted, a report may be submitted using the Adverse Event Expedited Report – Single Agent or Multiple Agents paper template (available on the CTEP Home Page at http://ctep.cancer.gov).

Templates must be faxed to CTEP at 301-230-0159.

When Internet connectivity is restored, a report submitted on a paper template must be entered into electronic AdEERS by the original submitter of the report at the site. All expedited AE reports must also be sent to the local Institutional Review Board (IRB) according to local IRB's policies and procedures.

All AEs reported via AdEERS must also be reported via the routine AEs reporting defined by the protocol.

All Cooperative Groups trials must use AdEERS for expedited reporting of AEs resulting from:

- Trials utilizing a commercial agent only;
- Trials utilizing an investigational agent under a CTEP IND and a commercial agent on separate arms;
- Trials utilizing an investigational agent under a CTEP IND and a commercial agent on the same arm.

3.2.2 Expedited Adverse Event Reporting of Hospitalization or Prolongation of Existing Hospitalization for all Phases of Trials

CTEP defines hospitalization for expedited AE reporting purposes as an inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where the adverse event truly fits this definition and not for hospitalizations associated with less serious events. For example, a hospital visit where a patient is admitted for observation or minor treatment (e.g., hydration) and released in less than 24 hours. Furthermore, hospitalization for pharmacokinetic sampling, is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report.

Hospitalization or prolongation of hospitalization associated with Grade 3 events, unexpected and expected, and regardless of attribution; require expedited reporting for trials utilizing an agent under a CTEP IND.

3.2.2.1 24-Hour Notification for CTEP IND Trials

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is

expected or unexpected, the grade and attribution. Table C and Table D outline 24-hour notification to CTEP for AEs that occur on trials utilizing an agent under a CTEP IND.

Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS at http://ctep.cancer.gov.

To ensure vigilance for AEs that require 24-hour notification, AdEERS is programmed to facilitate complete, timely submission. Initiation of an AdEERS report via the 24-Hour Pathway generates these events:

1. When the Reporter Information screen is saved, an e-mail is submitted to the Reporter indicating the initiation of an AdEERS report.
2. Submission of a 24-hour notification is only the beginning of the requirement for a complete AdEERS report, and the 5-day clock commences. The complete report must be submitted to CTEP, NCI within 5 calendar days.
3. On calendar day 3, if the complete report has not been submitted, a system-generated email is sent to the Reporter, to the local treating physician, to the Study PI, and to the Lead Group Coordinator (where applicable). The message is a reminder that the complete report associated with a 24-hour notification is due in 2 calendar days.
4. On calendar day 6, if the complete report has not been submitted, a system-generated email is sent to the Reporter, to the local treating physician, to the Study PI, and to the Lead Group Coordinator (where applicable) This second message reminds recipients that the complete report associated with a 24-hour notification is overdue.
5. On calendar day 8, if the complete report has not been submitted, a final email is sent to the Reporter, to the local treating physician, to the Study PI, to the Lead Group Coordinator (where applicable) and to CTEP. Personal correspondence from CTEP will follow. The incomplete report initiated by a 24-hour notification will be flagged by the system as 'Initiated, not submitted', and although no longer accessible in the system, it is available for audit purposes.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to CTEP by telephone at 301-897-7497.

3.2.2.2 24-Hour Notification for non-CTEP IND Trials

Cooperative Groups have the option to use the AdEERS 24-Hour pathway for all Group trials. However, 24-hour notifications for non-CTEP IND trials will go only to the Lead Group Coordinator, not to CTEP, NCI. The automatic electronic reminders are not operative in the 24-hour pathway for non-CTEP IND trials. To avoid congestion of the AdEERS system, incomplete non-CTEP IND reports initiated with a 24-hour notification will be withdrawn on calendar day 8.

3.3 Routine and Expedited Reporting Requirements for Specialized Adverse Events

3.3.1 Reporting Requirements for Baseline Adverse Events

Although a pertinent positive finding identified on baseline assessment is not an 'AE,' when possible it is to be documented as 'Course Zero' using CTC/CTCAE terminology and grade. An expedited AE report is not required if a patient is entered on a protocol with a pre-existing condition (e.g., elevated laboratory value, diarrhea). The baseline AE must be re-assessed throughout the trial and reported if it fulfills expedited AE reporting guidelines.

1. If the pre-existing condition worsens in severity, the investigator must reassess the event to determine if an expedited report is required (assign attribution and refer to Table C or Table D).
2. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required (assign attribution and refer to Table C or Table D).
3. No modification in grading is to be made to account for abnormalities existing at baseline.

For example, in a clinical situation when a patient enters a Phase 1 or Phase 2 trial utilizing an agent under a CTEP IND with an AST/SGOT equivalent to CTC/CTCAE Grade 1:

1. ROUTINE reporting of AST/SGOT is not required for Cycle 1.
2. EXPEDITED reporting requirements (Table C and Table D) depend on:
    a. If the AST remains unchanged while on study, AdEERS is not required. An expedited AE report is not to be submitted.
    b. If at any time while on study the AST/SGOT value increases equivalent to Grade 2:
        - The investigator determines that AST/SGOT is unexpected as defined by the protocol and the attribution to the investigational intervention is at least possible, an AdEERS report is required.
        - The investigator determines that AST/SGOT is unexpected as defined by the protocol and the attribution to the investigational intervention is unrelated or unlikely, an AdEERS report is not required.
        - The investigator determines that AST/SGOT is expected as defined by the protocol. Therefore, regardless of attribution to the investigational intervention, an AdEERS report is not required.
    c. If at any time on study the AST/SGOT value increases equivalent to Grade 3 and is associated with hospitalization and/or prolongation of hospitalization:
        - An AdEERS report is required regardless of unexpected/expected and regardless of attribution.
    d. If at any time while on study the AST/SGOT value increases equivalent to Grade 3 and is not associated with hospitalization and/or prolongation of hospitalization:
        - The investigator determines that AST/SGOT is unexpected as defined by the protocol and the attribution to the investigational intervention is at least possible, an AdEERS report is required.
        - The investigator determines that AST/SGOT is unexpected as defined by the protocol and the attribution to the investigational intervention is unrelated or unlikely, an AdEERS report is not required.
        - The investigator determines that AST/SGOT is expected as defined by the protocol. Therefore, regardless of attribution to the investigational intervention, an AdEERS report is not required.

3.3.2 Reporting Requirements for Persistent/Recurring Adverse Events

Persistent Adverse Events:

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses.

Routine reporting: The event must be reported only once unless the grade becomes more severe in a subsequent course. If the grade becomes more severe the AE must be reported again with the new grade.

Expedited reporting: The event must be reported only once unless the grade becomes more severe in the same or a subsequent course.

Recurring Adverse Events:

A recurring AE is one that occurs and resolves during a cycle/course of therapy and then reoccurs in a later cycle/course.

Routine reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported by the routine procedures.

Expedited reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require AdEERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

Example of persistent/recurring AE:

CTCAE v3.0	Grade 1	Grade 2	Grade 3	Grade 4
Platelets	<LLN – 75,000	<75,000 – 50,000	<50,000 – 25,000	<25,000

Example of reporting requirements (routine and expedited) of the AE 'Platelets' on a protocol where Platelets is an *unexpected* event and hospitalization is *not* associated with the Platelet count:

Cycle 1 Platelet count 40,000 = Grade 3
Both routine CDUS report and expedited AdEERS report **are** required
- Platelet count remains at Grade 2 at end of Cycle 1

Cycle 2 Platelet count 50,000 = Grade 2 (persistent AE)
Both routine CDUS and expedited AdEERS reports are **not** required
- Platelet count resolved at end of Cycle 2

Cycle 3 Platelet count 24,000 = Grade 4 (Recurrent AE with increased Grade)
Both routine CDUS report and expedited AdEERS report **are** required
- Platelet count equivalent to Grade 1 at end of Cycle 3

Cycle 4 Platelet count 24,000 = Grade 4 (Recurrent AE with same Grade)
Routine CDUS reporting **is** required. Expedited AdEERS reporting is **not** required.

Important: An expedited report (AdEERS) is required for Grade 3 or higher AEs with hospitalization or prolongation of hospitalization at any time, regardless of persistent/recurring AEs.

3.3.3 Reporting Requirements for Adverse Events experienced in a Clinical Trial utilizing Investigational Agent(s) and Commercial Agent(s) on Separate Arms under a CTEP IND

3.3.3.1 Routine Reports

Routine AE reporting for Phase 1 and Phase 2 clinical trials using an investigational agent and a commercial agent on separate arms is via either CTMS or CDUS as stated in the protocol.

Routine AE reporting for Phase 3 clinical trials using an investigational agent and a commercial agent on separate arms must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators.

3.3.3.2 Expedited Reports

An event that occurs on an arm using an investigational agent (agent under an IND) must be assessed in accordance with the guidelines for investigational agents in Table C and Table D, and where indicated, an AdEERS report must be submitted.

An event that occurs on an arm using a commercial agent must be assessed as specified in the protocol. In general, only Grade 4 and 5 events that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.

Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via AdEERS. In general, only Grade 4 and 5 events that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions. AdEERS is programmed to automatically submit the report to FDA. CTEP does not review commercial agent only expedited reports.

3.3.4 Reporting Requirements for Adverse Events experienced in a Clinical Trial utilizing Investigational Agents in combination with Commercial Agent(s) on the same arm

Note: The combination of an investigational agent with a commercial agent under a CTEP IND is considered investigational.

3.3.4.1 Routine Reports

Routine AE reporting for Phase 1 and Phase 2 clinical trials using an investigational agent in combination with a commercial agent is via either CTMS or CDUS as stated in the protocol.

Routine AE reporting for Phase 3 clinical trials using an investigational agent and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators

3.3.4.2 Expedited Reports

An event that occurs on a combination trial must be assessed in accordance with the guidelines for investigational agents in Table C and Table D, and where indicated, an AdEERS report must be submitted.

An event that occurs prior to administration of the investigational agent must be assessed as specified in the protocol. In general, only Grade 4 and 5 events that are unexpected with at least possible

attribution to the commercial agent require an expedited report. Refer to each protocol for specific AE reporting requirements or exceptions.

Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via AdEERS.

An investigational agent might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected event (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

3.4 Trials utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events Based on Phase of Trial

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[1] of the Last Dose of the Investigational Agent on Phase 1 Trials

	1	2	2	3		3		4 & 5[2]
	Unexpected and Expected	Unexpected	Expected	Unexpected		Expected		Unexpected and 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	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

[1]**Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> 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

[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.

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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[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

	1	2	2	3		3		4 & 5	4 & 5[2]
	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

[1]**Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> 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

[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.

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3.5 Exceptions for Expedited Reporting

An expedited report may not be required for a specific protocol where an AE is listed as expected. The exception or acceptable reporting procedures must be specified in the text of the protocol. The protocol specific guidelines supersede the CTEP, NCI Adverse Event Reporting Guidelines (Table C and Table D) for AE reporting.

3.5.1 Persistent or Significant Disabilities/Incapacities

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies or birth defects, must be reported via AdEERS if they occur at any time following treatment with an agent under a CTEP IND.

3.5.2 Death

Death occurring after the last dose of an agent under a CTEP IND agent must be submitted via AdEERS within the timelines outlined in Table C and Table D.

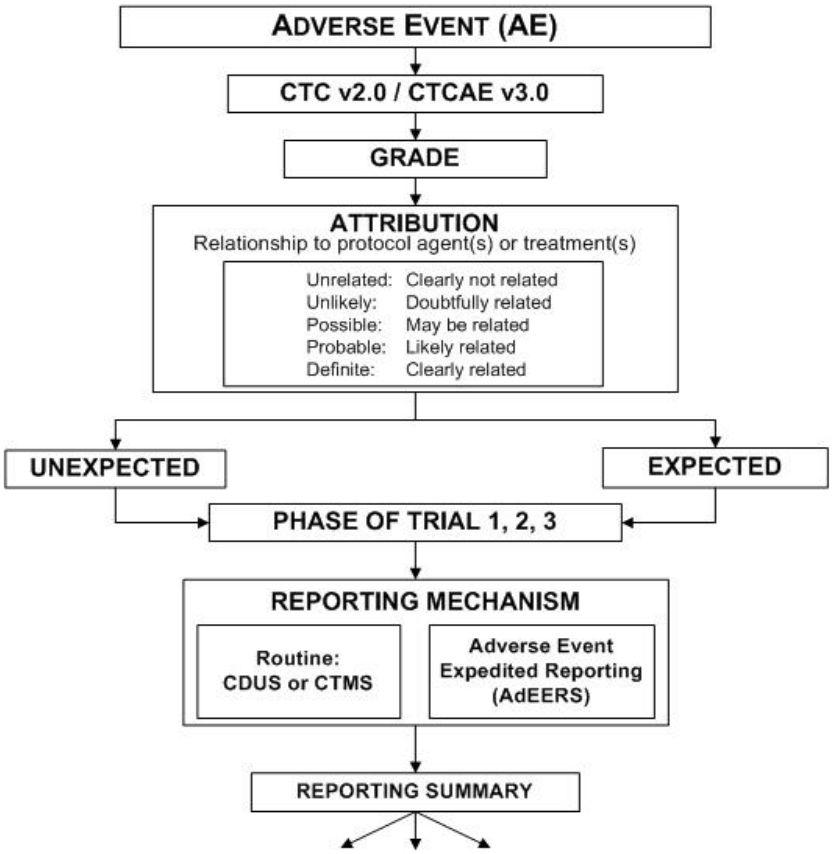
1. Any death occurring within 30 days of the last dose, regardless of attribution to an agent under a CTEP IND.

   Important: An AdEERS 24-hour notification is not required for death clearly related to progressive disease.

2. Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent under a CTEP IND.

ATTACHMENT A: THE ADVERSE EVENT REPORTING REQUIREMENT PARADIGM FOR AGENTS UNDER A CTEP IND

The following describes the process for determining if an adverse event is reportable to CTEP, NCI.



	GRADE 1		GRADE 2		GRADE 3		GRADE 4		GRADE 5	
ATTRIBUTION	**UNEXPECTED**	**EXPECTED**	**UNEXPECTED**	**EXPECTED**	**UNEXPECTED**	**EXPECTED**	**UNEXPECTED**	**EXPECTED**	**UNEXPECTED**	**EXPECTED**
UNRELATED	CTMS	CTMS	CTMS	CTMS	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
UNLIKELY	CTMS	CTMS	CTMS	CTMS	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
POSSIBLE	CTMS CDUS	**CTMS CDUS**	CTMS CDUS AdEERS	**CTMS CDUS**	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
PROBABLE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS
DEFINITE	CTMS CDUS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS	CTMS CDUS AdEERS

CDUS – CLINICAL DATA UPDATE SYSTEM for Routine Reporting

CTMS – CLINICAL TRIALS MONITORING SERVICE for Routine Reporting

AdEERS – EXPEDITED REPORTING (This includes hospitalization [or prolongation of existing hospitalization] for any event equivalent to CTC Grade 3, 4, 5 which precipitated hospitalization regardless of requirements for Phase of study, expected or unexpected, and attribution.)