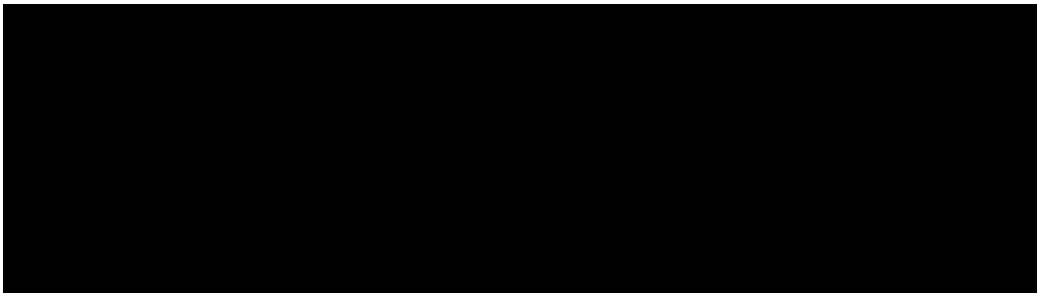

NCI GUIDELINES FOR INVESTIGATORS: ADVERSE EVENT REPORTING REQUIREMENTS

Effective February 25, 2011

AdEERS Medical Help Desk Contact Information:
Phone: 301.897.7497
Fax: 301.230.0159
E-mail: adeersmd@tech-res.com

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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/interventions and the monitoring of serious adverse events (21 CFR 312). The Cancer Therapy Evaluation Program (CTEP) the Cancer Imaging Program (CIP) under the Division of Cancer treatment and Diagnosis (DCTD), and the Division of Cancer Prevention (DCP) of the National Cancer Institute (hereafter referred to as NCI in this document), sponsor an extensive national program of cancer research as both an Investigational New Drug application (IND)/Investigational Device Exemption (IDE) sponsor and/or a funding sponsor and is responsible for ensuring that the research is conducted in accordance with Federal Regulations.

The guidance provided herein, for all DCTD-sponsored studies that fall under an FDA Investigational Device Exemption (IDE), is specific to NCI CTEP/CIP. FDA regulations (21CFR 812) must be consulted for such trials. In applying this Guideline document to IDE studies, all IND (21 CFR 312) specific references and terms should be converted to the comparable IDE (21 CFR 812) term (e.g. "device" "UADE"), as applicable.

1.1. Scope

This document applies to all NCI, CTEP-funded and/or sponsored clinical studies, including those sponsored by Cooperative Groups, as well as studies sponsored by the CIP.

This document applies to all agents/interventions specified in the study as requiring adverse event reporting to NCI.

1.2. Purpose

The primary purpose of this document is to:

- Provide guidelines for adverse event (AE) reporting to NCI for agents provided under a CTEP or CIP IND/IDE.
- Ensure that sufficient AE information is submitted by the site to allow for an independent assessment by CTEP, DCP, and CIP as IND/IDE sponsors.

A second purpose of this document is to explain the expanded use of AdEERS for expedited AE reporting for Cooperative Group trials. All Cooperative Groups **MUST** use AdEERS.

A third purpose of this document is to describe new expedited reporting requirements for new CTEP and CIP INDs/IDEs studies, as well as CIP non-IND/IDE studies. Studies will be assigned a specific table by NCI.

1.3. Investigator Responsibility

- Clinical investigators and ultimately the protocol Principal Investigator (PI) have the primary responsibility for AE identification, documentation, grading, and assignment of attribution to the investigational agent/intervention.
- It is the responsibility of the investigators to supply the medical documentation needed to support the expedited AE reports in a timely manner. Failure to provide the requested information may result in the termination of the study.
- To promptly report to the sponsor any AE that may reasonably be regarded as caused by, or probably caused by, the drug/device. If the AE is serious, the investigator shall report the AE immediately (21 CFR 312.64b, 21 CFR 812). This can be accomplished following the expedited reporting guidelines herein.

1.4. Sponsor Responsibility

- It is the responsibility of the sponsor to submit an IND/IDE for clinical trials conducted with investigational agents/interventions subject to FDA 21 CFR 312 and 21 CFR 812, and to ensure that FDA and all participating investigators are promptly informed of significant new AE's or risks with respect to the drug/device (21 CFR 312.50, 21 CFR 812).
- The sponsor shall notify the FDA and all participating investigators in a written IND Safety Report, as specified in FDA 21 CFR 312.32, or 21 CFR 812 for an IDE:

- Any adverse experience associated with the use of the investigational agent/intervention that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggest a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

In the Annual Report to the IND/IDE, the sponsor shall submit a summary of the previous year's clinical investigations; including most frequent and most serious AEs, IND and IDE safety reports, subjects who died (with the cause of death), and subjects who dropped out in association with an AE, whether or not thought to be drug/device related (see 21 CFR 312.33 or 21 CFR 812 for more details).

2.0 Tools for AE Reporting:

2.1 Basic Terminology:

2.1.1 **Adverse Event (AE or Adverse Experience):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of 'unrelated', 'unlikely', 'possible', 'probable', or 'definite'). (ICH E2A, E6).

2.1.2 **Attribution:** An assessment of the relationship between the AE and the medical intervention**.** CTCAE does not define an AE as necessarily "*caused by a therapeutic intervention"*. After naming and grading the event, the clinical investigator must assign an attribution to the AE using the following attribution categories:

RELATIONSHIP	ATTRIBUTION	DESCRIPTION
Unrelated to investigational agent/intervention[1]	Unrelated	The AE *is clearly **NOT** related* to the intervention
	Unlikely	The AE *is **doubtfully related*** to the intervention
Related to investigational agent/intervention[1]	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

[1]**NOTE**: AEs listed as 'possibly, probably, or definitely' related to the investigational agent/intervention in AdEERS are considered to have a suspected 'reasonable causal relationship' to the investigational agent/intervention (ICH E2A). For routine, CDUS adverse event reporting purposes, "Attribution" defines the relationship between the adverse event and the investigational agent(s)/intervention as defined in CDUS and CDS Instructions and Guidelines that can be found at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/cdus_ig_3r4.pdf. For assistance please contact adeersmd@tech-res.com.

2.1.3 **CAEPR: The Comprehensive Adverse Events and Potential Risks List** was introduced in August 2004. The CAEPR is an NCI-generated list of reported and/or potential AEs associated with an agent currently under an NCI IND/IDE. Information contained in the CAEPR is compiled from the IB, the Package Insert (for those investigational agents that are available commercially), the Instructions for Use (IFU - for a device), as well as company safety reports, AEs submitted through AdEERS, and peer-reviewed publications that contain safety information not contained in the current IB or Package Insert.

2.1.4 **Cancer Adverse Event Reporting System (caAERS):** Is an open source software tool that is used to collect, process, and report adverse events that occur during clinical trials. This tool supports regulatory and protocol compliance for adverse event reporting and allows local collection, management, and querying of adverse event data, whether routine or serious. This tool also supports service based integration of data from other clinical trials management systems. (See https://cabig.nci.nih.gov/tools/caAERS) On a case-by-case basis this system may be used in place of AdEERS.

2.1.5 Commercial Agent: A commercial agent is one approved by the FDA for commercial distribution. Please note that a commercial agent may be used in a clinical study for its FDA-approved indication as a non-investigational agent, for an off-label use, or as an IND (investigational) agent. Refer to the protocol document to determine whether or not a commercially-available agent is being used as an investigational agent, for that particular protocol.

2.1.6 CTCAE: The NCI Common Terminology Criteria for Adverse Events (CTCAE) provides a descriptive terminology that is to be utilized for AE reporting. A grading (severity) scale is provided for each AE term. CTCAE is described more fully below in Section 2.2

2.1.7 Expectedness: An unexpected AE is any AE, the specificity or severity of which is not consistent with the current IB, or the Instructions for Use or other device documentation; or, if an IB or equivalent is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the IND/IDE (21 CFR 312.32 and/or 21 CFR 812). Additionally the ICH E2A defines an unexpected adverse drug reaction as an AE, the nature and severity of which is not consistent with the applicable product information (for example, Investigator's Brochure for investigational agent). The investigator shall report all SAE's immediately to the sponsor except for those that the protocol or IB identifies as not requiring immediate reporting (EC Directive of 2001; Article 16, #1).

2.1.7.1 <u>For NCI IND/IDE Agents/interventions</u>: Any AE listed in the SPEER should be considered expected for the purposes of expedited reporting to NCI. Everything else should be considered unexpected for expedited AE reporting purposes, unless specifically stated otherwise in the protocol document.

2.1.7.2 For Commercial Agents not under a NCI IND/IDE: Any AE, the specificity or severity of which is consistent with the current IB, product label, and/or the protocol document.

2.1.8 Expedited Reporting: Any AE that is both serious and unexpected qualifies for expedited reporting timelines to the sponsor (for timelines, see 21 CFR 312. 32 and ICH E6). To ensure compliance with these regulations/guidances, as IND/IDE sponsor, NCI requires that AEs be submitted to them according to the timeframes in the AE reporting table assigned to the protocol (i.e., Appendix 1 (for NCI investigational agents/devices, Appendix 2 (for CIP commercial agents), as well as any specific protocol inclusions/exclusions. These AEs are to be submitted to NCI via AdEERS (see Section 4.0). Requirements for devices may differ and the protocol should be followed in such cases.

2.1.9 Hospitalization (or prolongation of hospitalization): NCI 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 AE and should **ONLY** be used for situations where the AE 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.

2.1.10 Investigational Device Exemption (IDE): An **IDE** allows the investigational device (a medical device that is undergoing clinical trials to evaluate safety and effectiveness) to be used in a clinical protocol in order to collect safety and effectiveness data required to support a Premarket Approval (PMA) application or a Premarket Notification [510(k)] submission to Food and Drug Administration (FDA).

NOTE: IDEs are regulated under 21 CFR 812, and this part must be consulted, for all studies that include a qualifying device, as some requirements (e.g. UADE and other FDA IDE reporting) may differ from or exceed NCI requirements, as specified herein.

2.1.11 Investigational New Drug (IND): Refers to any drug or biological drug that is used in a clinical investigation. Synonymous with *Investigational drug* (FDA 21 CFR 312.3). This includes a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, when used for an unapproved indication, or when used to gain further information about an approved use (Guideline for Good Clinical Practice Section 1.33).

2.1.12 Investigator (Principal Investigator): An individual who actually conducts a clinical investigation (i.e., under whose immediate direction the investigational agent/intervention is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team (21 CFR 312.3)

2.1.13 Investigator's Brochure (IB): A compilation of the clinical and nonclinical data on the investigational drug(s) that is relevant to the study of the investigational drug(s) in human subjects (FDA 21 CFR 312.23, ICH E6).

2.1.14 Institutional Review Board (IRB): Any board, committee, or other group formally designated by an institution to review biomedical research involving human subjects, to approve the initiation of, and conduct periodic review of such research. The term is synonymous with *institutional review committee.* (FDA 21 CFR 50, ICH 6A).

2.1.15 Health Insurance Portability and Accountability Act (HIPAA): HIPAA (enacted in 1996) was adopted to ensure health insurance coverage after leaving an employer and also to provide standards for facilitating health care-related electronic transactions.

2.1.16 Life-Threatening Adverse Event or Life Threatening Suspected Adverse Reaction: Any AE that places the subject, in the view of either the investigator or the sponsor (NCI), at immediate risk of death from the AE as it occurred. It does **NOT** include an AE that, had it occurred in a more severe form, might have caused death. (FDA 21 CFR 312.32, ICH E2A).

2.1.17 Medical Dictionary of Regulatory Affairs (MedDRA): A clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process developed by the International Conference on Harmonization (ICH)

2.1.18 MedWatch: The Food and Drug Administration**'s** reporting system for **AEs,** founded in 1993**.** The MedWatch system is intended to detect safety hazard signals for medical products. If a signal is detected, the FDA can issue medical product safety alerts or order product recalls, withdrawals, or labeling changes to protect the public health. Important safety information is disseminated to the medical community and the general public via the MedWatch web site. AEs can be reported on a single, one-page reporting form (Form FDA 3500 or 3500A). Reporting can be conducted online by phone (1-800-FDA-1088) or by submitting the MedWatch Form 3500 or 3500A by mail or fax (1-800-FDA-0178). The link for electronic submission of AEs for commercial agents via the MedWatch Form 3500 or 3500A is: https://www.accessdata.fda.gov/scripts/medwatch/medwatch-online.htm.

2.1.19 Pharmaceutical Data Sheet (PDS): Description of the investigational agent's physical, chemical and pharmaceutical properties, prepared by CTEP's Pharmaceutical Management Branch (PMB).

2.1.20 Second Malignancy: A cancer that is unrelated to the treatment of a prior malignancy and is not a metastasis from the initial malignancy.

2.1.21 Secondary Malignancy: A cancer caused by treatment for a previous malignancy (e.g., treatment with radiation or chemotherapy). It is NOT considered a metastasis of the initial malignancy.

2.1.22 Serious Adverse Event (SAE): Any adverse drug event (experience) occurring at any dose that in the opinion of either the investigator or sponsor results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse drug experience.
3) Inpatient hospitalization or prolongation of existing hospitalization (for >24 hours).
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

2.1.23 Specific Protocol Exceptions to Expedited Reporting (SPEER): Is a subset of AEs within the CAEPR that contains **ONLY** AEs that are to be considered **EXPECTED** for AdEERS reporting

purposes (See Section 2.3 for CAEPR information). Formerly referred to as the Agent Specific Adverse Event List (ASAEL).

2.1.24 Sponsor: The individual, pharmaceutical company, government agency (NCI), academic institution, private organization, or any other organization who takes responsibility for and initiates a clinical investigation. The sponsor does not have to actually conduct the investigation. (21 CFR 312.3)**.**

2.1.25 Unanticipated Adverse Device Event (UADE): "Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects" (21 CFR 812.3[s]). UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE to the sponsor [NCI] and the reviewing IRB as soon as possible, **but in no event later than 10 working days after the investigator first learns of the event** (21 CFR 812.150(a)(1)).
- Sponsors [NCI] must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect (21 CFR 812.46(b), 812.150(b)(1)).

NOTE: **The IDE regulations, therefore, require sponsors to submit reports to IRBs in a manner consistent with the recommendations made above for the reporting of unanticipated problems under the IND regulations.**

2.2 Common Terminology Criteria for AEs (CTCAE):

Common Terminology Criteria for Adverse Events (CTCAE): Is designed as an instrument to be used to document AEs identified through a combination of clinical and laboratory evaluation. CTCAE is **NOT** a tool 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.

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT). Grade is an essential element of the Guidelines and, in general, relates to **severity** for the purposes of regulatory reporting to NCI as follows:

Grade	Description
0	**No AE** or within normal limits
1	**Mild**; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
2	**Moderate**; minimal, local, or noninvasive intervention (e.g., packing, cautery) indicated; limiting age-appropriate instrumental activities of daily living (ADL).
3	**Severe** or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
4	**Life-threatening** consequences; urgent intervention indicated.
5	**Death** related to AE

NOTE: A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in Section 2.1.22 (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

2.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List

Information contained in the CAEPR is compiled from the IB, the Package Insert (for those investigational agents that are available commercially) as well as company safety reports, AEs submitted through AdEERS, and peer-reviewed publications that contain safety information not contained in the current IB or Package Insert. The safety profile for an investigational agent is reviewed at least annually in accordance with cGCP guidelines. It may be amended

more frequently in response to an emerging safety profile for the agent/intervention, e.g., in conjunction with an Action Letter.

2.3.1 Studies Requiring the Inclusion of a CAEPR:

NCI requires the inclusion of a CAEPR in studies described below. Other studies can utilize the NCI CAEPR as well.

- For all studies conducted under a NCI IND.
- For all studies reviewed by CTEP/CIP that includes investigational agents/interventions for which NCI has a CAEPR.

2.3.2 As the CAEPR is updated the SPEER is also revised and the revisions will be sent to all Principal Investigators registered to NCI-approved studies using the agent(s). A copy of the current CAEPR (containing the SPEER) may also be obtained via email from PIO@CTEP.NCI.NIH.GOV.

2.4 HIPAA

The increased use of electronic medical records has increased the potential for individuals to access, use, and disclose sensitive personal health data. The U.S. Department of Health and Human Services (DHHS) addressed these concerns with new privacy standards that set a national minimum of basic protections, while balancing individual needs with those of society. To improve the efficiency and effectiveness of the health-care system, HIPAA required DHHS to adopt national standards for electronic health-care transactions. The HIPAA Privacy Rule regulates how certain entities, called covered entities, use and disclose certain individually identifiable health information, called protected health information (PHI). Therefore, the Privacy Rule expressly permits PHI to be shared for specified public health purposes. For example, covered entities may disclose PHI, without individual authorization, to a public health authority legally authorized to collect or receive the information for the purpose of preventing or controlling disease, injury, or disability (45 CFR 164.512[b]). (See Appendix 4 and 5)

3 Routine AE Reporting to NCI: Scope:

3.1 Clinical Data Update System (CDUS):

Any adverse event (routine or expedited) meeting the requirements described in either Table A or Table B, **MUST** be reported to NCI via the CDUS, CTMS or C3D data collection mechanism if the NCI has assigned the CDUS-Complete data reporting. If the study is assigned to CDUS-Abbreviated data reporting, no adverse event reporting (routine or expedited) is required via any of the CDUS mechanisms. As these data collection mechanisms are the primary source of clinical data for the NCI, all NCI sponsored trials are assigned to either CDUS-Abbreviated reporting or CDUS-Complete reporting during the review process. Specific details about CDUS reporting requirements can be found at: http://ctep.info.nih.gov/protocolDevelopment/electronic_applications/docs/cdus_ig_3r4.pdf.

Table A: CDUS Guidelines for Routine Event Reporting on Studies using Agent(s) under a NCI 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

3.2 Clinical Trials Monitoring System (CTMS)

The CTMS is maintained by a non-Governmental organization contracted by NCI to receive, review and perform data management tasks on individual patient case report forms for Phase 1 investigational agent/intervention

studies designated by NCI for such monitoring. Information regarding submitting AE reports via CTMS can be found at: http://www.theradex.com/CTMS/Default.aspx.

Table B: CTMS Guidelines for Routine Adverse Event Reporting for Studies using Agent(s) under a NCI 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

3.3 C3D

C3D is a clinical trial data management system that is used on some studies to enter and process both adverse event and study data. On some IND trials C3D may be designated during the design or implementation phase as the method for collection and reporting requirements for Adverse Events. For purposes of this document, C3D may be used, as specified in the protocol, in lieu of the CDUS complete dataset, for this purpose. Trials using C3D still must use the AdEERS system, as specified herein, to report events that qualify for AdEERS reports.

4 Expedited AE Reporting to NCI: Scope

4.1 Adverse Event Expedited Reporting System (AdEERS)

NCI's original web-based system for electronic submission of expedited reports on studies utilizing an NCI sponsored IND was published in 1998. The current version of AdEERS allows Cooperative Groups to report AEs for their studies, including those not under a NCI IND/IDE, commercial agent-only, investigational agent/intervention and commercial agent on separate arms, or investigational agent/intervention and commercial agent on the same arm. **PLEASE NOTE**: Expedited reports submitted by Cooperative groups for non-NCI IND/IDEs will neither be reviewed nor submitted to the FDA by NCI. This is the responsibility of the IND/IDE sponsor(s) of those studies. For instances wherein CTEP is supplying an investigational agent to be used under a non- CTEP IND (e.g., a Cooperative Group IND or an Investigator IND), copies of all IND Safety Reports submitted to the FDA per 21 CFR 312.32 should be forwarded to CTEPSupportAE@tech-res.com.

New expedited reporting requirement tables for NCI IND/IDE studies as well as CIP studies are now available for new studies, and can be found in Appendices 1 and 2. The tables represent a reporting scale in compliance with 21 CFR 312.64, in order to more closely tailor the reporting needs of a protocol based on (1) the extent of clinical experience with the agent(s), (2) the need to maintain patient safety and regulatory compliance, and (3) the NCI medical monitors' collective medical experience. These tables cover the spectrum from Phase 0 through Phase 3 studies and for studies that include a treatment arm consisting commercial- agent(s) only. In general, a table will be assigned by NCI as follows:

Tables for Appendix 1 (CTEP Studies)

(Legacy Table C) Reporting Requirements for Adverse Events that Occur within 30 days of the Last Dose of Investigational Agent on Phase 1 Studies

(Legacy Table D) Requirements for Adverse Events that Occur within 30 days of the Last Dose of Investigational Agent on Phase 2 and 3 Studies

NOTE: Protocols approved prior to March 28, 2011 will continue to use these tables for AdEERS reporting requirements

Phase 0: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention

Phase 1/Early Phase 2: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention

Late Phase 2/Phase 3: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention

Table for Appendix 2 (CIP Studies)

Expedited Reporting Requirements for Adverse Events that Occur in a CIP commercial (non-IND/IDE) study.

PLEASE NOTE: The appropriate AE reporting table for a new protocol will be determined by NCI.

4.2 General Instructions for Expedited Reporting via AdEERS

- An expedited AE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via AdEERS at: https://webapps.ctep.nci.nih.gov/openapps/plsql/gader_accept$.startup .
- Adverse Events in an American College of Radiology Imaging Network (ACRIN) study should be reported as specified in the ACRIN protocol.
- Any Medical documentation supporting an expedited report (e.g., H &P, admission and/or notes, consultations, ECG results, etc.) **MUST** be faxed within 48-72 hours to the appropriate destination (see Appendix 3).
  NOTE: Submission of supporting medical information for non-NCI IND/IDE studies should be submitted to the Cooperative Group office
  NOTE: English is strongly recommended for supporting documentation submitted to the numbers listed below in order for the NCI to meet the regulatory reporting timelines.
  - CTEP studies: 301-230-0159 (back-up: 301-897-7404)
  - CIP studies: 301-897-7402
- Expedited AE reporting timelines are defined as:
  - "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
  - "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the patient and require intervention to prevent a serious AE, must be reported via AdEERS if the event occurs following investigational agent administration.
- **NOTE:** All deaths that occur after the last dose of a study agent/intervention under an NCI IND/IDE on study require regardless of causality. An attribution to the study agent/intervention administration or to some other contributing cause **MUST** be provided. Any death occurring greater than 30 days after the last dose of investigational agent/intervention with an attribution of possible, probable or definitely due to the agent/intervention must be reported to NCI even if the patient is off study.
- AdEERS Medical Questions/Help: *email:* adeersmd@tech-res.com, *phone:* (301) 897-7497, *fax:* (301) 230-0159

- Technical Questions/Help (e.g. IT issues, system problems, etc.)/: *email:* ncictephelp@ctep.nci.nih.gov, *phone:* 1-888-283-7457 or 301-840-8202.
- AdEERS Frequently Asked Questions (FAQ): https://webapps.ctep.nci.nih.gov/ctep-html/adr_faq.htm
- AdEERS Computer Based training: http://ctep.cancer.gov/reporting/AdEERS_CBT_v3/start.html

4.2.1 Expedited AE Reporting of Hospitalization or Prolongation of Hospitalization for all Phases of Trials: NCI 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 AE and should **ONLY** be used for situations where the AE truly fits this definition and **NOT** for hospitalizations associated with less serious events (e.g., hospital visits 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.

4.2.2 24-hour Notification: The AE 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 AE is expected or unexpected, and the grade and attribution. Appendices 1 and 2 outline the requirements for 24-hour notification to NCI for AEs that occur on trials utilizing an agent under a NCI IND/IDE.

4.2.2.1 Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS at https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup.

4.2.2.2 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 expedited report.

2. Submission of a 24-hour notification is only the beginning of the requirement for a complete expedited report. The complete report **MUST** be submitted to NCI within 5 calendar days of the 24-hour notification.

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 NCI. Personal correspondence from NCI 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.

6. In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made to NCI by telephone at: **301-897-7497,** or 301-897-7402 for CIP studies**.** An electronic report **MUST** be submitted immediately upon re-establishment of internet connection.

4.2.2.3 24-hour Notification for non-CTEP IND/IDE Trials:

Cooperative Groups have the option to use the AdEERS 24-Hour pathway for all Group trials. However, 24-hour notifications for non-NCI IND/IDE 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-NCI IND/IDE trials. To avoid congestion of the AdEERS system, incomplete non-NCI IND/IDE reports initiated with a 24-hour notification will be withdrawn on calendar day 8.

5. Reporting Requirements for Specialized AEs

5.1 Baseline AEs:

Although a pertinent positive finding identified on baseline assessment is not an AE, when possible it is to be documented as 'Course Zero' using 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 study 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 Appendices 1 and 2).
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 Appendices 1 and 2).
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 study utilizing an agent under a CTEP IND/IDE with an Aspartate aminotransferase increased (AST) equivalent to CTCAE Grade 1 (**Note**::

ROUTINE reporting of AST via CDUS/CTMS is not required for cycle 1)

EXPEDITED reporting requirements (See Appendices 1 and 2) depend on:

- If the AST remains unchanged while on study, an expedited report is **NOT** required to be submitted.
- If at any time while on study the AST value increases equivalent to Grade 2:
  - The investigator determines that AST is unexpected as defined by the protocol and the attribution to the investigational intervention is at least possible, an expedited report is required.
  - The investigator determines that AST is unexpected as defined by the protocol and the attribution to the investigational intervention is unrelated or unlikely, an expedited report is **NOT** required.
  - The investigator determines that AST is expected as defined by the protocol. Therefore, regardless of attribution to the investigational intervention, an expedited report is **NOT** required.
- If at any time on study the AST value increases equivalent to Grade 3 and is associated with hospitalization and/or prolongation of hospitalization, an AdEERS report is required regardless of expectedness and regardless of attribution.
- If at any time while on study the AST value increases equivalent to Grade 3 and is **NOT** associated with hospitalization and/or prolongation of hospitalization:
  - The investigator determines that AST is unexpected as defined by the protocol and the attribution to the investigational intervention is at least possible, an expedited report is required.
  - The investigator determines that AST is unexpected as defined by the protocol and the attribution to the investigational intervention is unrelated or unlikely, an expedited report is **NOT** required.

The investigator determines that AST is expected as defined by the protocol. Therefore, regardless of attribution to the investigational intervention, an expedited report is **NOT** required.

5.2 Persistent/Recurring AEs

Persistent AE:

A persistent AE is one that extends continuously, without resolution between treatment cycles/courses. **ROUTINE** reporting: The AE 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 AE must be reported only once unless the grade becomes more severe in the same or a subsequent course.

Recurrent AEs

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
2) Hospitalization is associated with the recurring AE.

Example of persistent/recurring AE:

CTCAE TERM	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 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 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 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 is required for unexpected Grade 3 or higher AEs with hospitalization or prolongation of hospitalization at any time, regardless of persistent/recurring AEs except for where designated in tables in Appendices 1 and 2.

5.3 AEs experienced utilizing Investigational Agent(s) and Commercial Agent(s) on Separate Arms

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention 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 studies using an investigational agent/intervention 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.

Expedited Reporting

- An AE that occurs on an arm using an investigational agent /intervention under an IND/IDE must be assessed in accordance with the guidelines for investigational agents in Appendix 1 for CTEP agents and Appendix 2

for CIP commercial agents, and where indicated, an expedited report must be submitted.

- An AE that occurs on an arm using a commercial agent on a separate treatment arm must be assessed as specified in the protocol**.** Only AEs MedWatch reporting requirements (refer to package insert) should be reported. **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. AdEERS is programmed to automatically submit the reports for AEs due to commercial agent(s) with a possible, probable, or definite attribution and ALL Grade 5 AEs regardless of attribution to the FDA via MedWatch. See link for submitting MedWatch Form 3500 or 3500A in Section 2.1.19.

5.4 AEs experienced utilizing Investigational Agents and Commercial Agent(s) on the SAME arm

NOTE: The combination of an investigational agent with a commercial agent under a NCI IND/IDE is considered investigational.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is via either CTMS or CDUS as stated in the protocol.
- Routine AE reporting for Phase 3 clinical studies using an investigational agent/intervention and a commercial agent in combination must be reported as defined by the general guidelines provided by sponsors, Groups, Cancer Centers, or Principal Investigators.

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting to CDUS

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP investigational agents/interventions in Appendix 1 and CIP commercial agents in Appendix 2, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs 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/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

5.5 Special Situations 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 NCI Adverse Event Reporting Guidelines (See Appendix 1 for CTEP investigational agents and see Appendix 2 for CIP commercial agents) for AE reporting.

5.5.1 Persistent or Significant Disabilities/Incapacities

Any AE 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 NCI IND/IDE.

5.5.2 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an NCI IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an NCI IND/IDE requires expedited reporting within 24-hours.

▪ Reportable categories of Death (not associated with a CTCAE term)

- Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
- Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: An unexpected cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

IMPORTANT: An AdEERS 24-hour notification is not required for death clearly related to progressive disease; however, a 10 calendar day report is required.

5.5.3 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AdEERS. Three options are available to describe the event:
    - Leukemia secondary to oncology chemotherapy
    - Myelodysplastic syndrome
    - Treatment related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

5.5.4 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS.

Appendix 1 Expedited Reporting Requirements for NCI IND/IDE Agents:

Legacy Tables C and D are to be used <u>ONLY</u> for protocols approved prior to March 28, 2011

Legacy Table C: Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 1 Studies

	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]AEs with attribution of, possible, probable, or definite that occur greater than 30 days after the last treatment with an agent/intervention under an NCI IND require reporting as follows:

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

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

[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.

Legacy 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 Studies

	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]AEs with attribution of, possible, probable, or definite that occur greater than 30 days after the last treatment with an agent/intervention under an NCI IND require reporting as follows:

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

- Grade 4 and Grade 5 unexpected AEs

AdEERS 10 calendar day report:

- Grade 3 unexpected AEs with hospitalization or prolongation of hospitalization
- Grade 5 expected AEs

[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.

Appendix 1 Expedited Reporting Requirements for NCI IND/IDE Agents:

Phase 0 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention[1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

Grade 1 and 2 Timeframes	Grade 3-5 Timeframes.
10 Calendar Days	24-Hour 5 Calendar Days

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]SAEs that occur **more than** 30 days after the last administration of investigational agent/intervention require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for **ALL** Grade 4 and 5 AEs and Grade 3 AEs with at least a possible attribution. [2]For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
1) A life-threatening adverse event
2) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
3) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
4) A congenital anomaly/birth defect.
5) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3-5 Timeframes</th></tr>
<tr><td>With Hospitalization ≥ 24 hrs</td><td rowspan="2">Not required</td><td>10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Without Hospitalization ≥ 24 hrs</td><td>Not required</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Appendix 1 Expedited Reporting Requirements for NCI IND/IDE Agents (cont.):

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>With Hospitalization ≥ 24 hrs</td><td rowspan="2">Not required</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Without Hospitalization ≥ 24 hrs</td><td>Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Appendix 2 Expedited Reporting Requirements for CIP Studies using Commercial Imaging Agent(s) ONLY

FOR USE IN CIP STUDIES INVOLVING COMMERCIAL (NON-IND/IDE) AGENTS ONLY

CIP Studies: Expedited Reporting Requirements for Adverse Events that Occur in CIP Non-IND/IDE studies within 30 Days of the Last Administration of a Commercial Imaging Agent [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the NCI via AdEERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>With Hospitalization ≥ 24 hrs</td><td rowspan="2">Not required</td><td colspan="2">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Without Hospitalization ≥ 24 hrs</td><td>Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via AdEERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Appendix 3 Contact Information for NCI Safety Reporting

Website for submitting expedited reports	https://webapps.ctep.nci.nih.gov/openapps/plsql/gadeers_main$.startup
AdEERSMD Help Phone (for CTEP)*	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
CIP Help Phone for SAE reporting*	301-897-1704 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Fax for expedited report supporting Medical Documentation for CTEP trials	301-230-0159 (back-up FAX: 301-897-7404)
Fax for expedited report supporting Medical Documentation for CIP trials	301-897-7402
AdEERSMD Help Email:	adeersmd@tech-res.com
CIP SAE Reporting Email	CIPSAEReporting@tech-res.com
Technical (e.g., IT or computer issues ONLY) Help Phone*	1-888-283-7457 or 301-840-8202
AdEERS Technical Help Email	ncictephelp@ctep.nci.nih.gov.
CTCAE v4 Help/Questions Email	ncictcaehelp@mail.nih.gov
AdEERS FAQs link	https://webapps.ctep.nci.nih.gov/ctep-html/adr_faq.htm
AdEERS Computer Based Training link	http://ctep.cancer.gov/reporting/AdEERS_CBT_v3/start.html

*Office phone and fax are accessible 24 hrs per day 7 days a week (The AdEERSMD phone line is staffed from Monday through Friday, 7:00 AM to 7:00 PM ET. Any phone call after these hours will go to voicemail. Please leave contact information and the phone call will be returned the following business day.

Appendix 4 HIPAA Memo (to accompany HIPAA document when requesting information)

Memorandum

To:

CC:

From:

Date:

Re: Instructions for HIPAA document

Please follow the instructions below.

STEP 1: When requesting PHI from an outside health care facility/provider, please complete the information on page 3 of the attached document entitled, "Request for Information on Patient Participating in a NCI Clinical Research Study."

STEP 2: Include your name and phone number as the requestor, the Patient's ID or medical record number, the emergency room visit and/or hospitalization dates, the information that you are requesting, and the date that the requested information is due back to you (refer to designated time frame on page 1 for the due date).

STEP 3: Forward the form along with the document on page 2 to the facility/provider

STEP 4: If the patient is deceased, please follow the instructions listed on page 2.

STEP 5: Once you have received the requested medical information, please follow the instructions that are listed on page 1.

For further assistance, please contact the AdEERSMD Help Desk by email: AdEERSMD@tech-res.com or by telephone at 301-897-7497.

Thank you for your time and cooperation in helping us with this vital research effort.

Appendix 5: HIPAA Document

Dear Investigator,

CTEP is required to meet Food and Drug Administration (FDA) established timelines when reporting adverse events from CTEP/DCTD/NCI-sponsored clinical trials. CTEP/DCTD/NCI-sponsored clinical research sites need to meet the designated timelines specified in the NCI Guidelines for reporting an Adverse Event. Please assist this process by:

- **sending the information below to the attention of: _____**
  CTEP requestor name
- **contacting the requestor for any questions at: _____**
  CTEP *requestor contact number*
- **forwarding the requested information listed below:**
- **write the following information** on **each page** that is faxed to **301- 230-0159**:

  Patient ID: _____
  AdEERS Ticket Number: _____

- **by the designated time frame: _____** utilizing the information listed below:
  Date

Please note that prior to sending the requested information to the CTEP requestor listed above; we request that the identifiers listed below be redacted/removed:

- Patient's name, postal address information, including: street address, city, county, precinct, zip code, and their equivalent geocodes
- Patient's Telephone Number(s)
- Patient's Social Security Number
- Patient's Medical Record Numbers
- Patient's Health Plan Beneficiary Numbers
- Patient's Account Numbers
- Patient's full-face photographic images and any comparable images

If you must obtain Protected Health Information (PHI) from an outside health care facility/provider: Please complete the information on the attached document labeled "Request for Information on Patient Participating in Clinical Research Study", including your name and phone number as the requestor, the patient's name, emergency room visit/hospitalization dates, the information required, and the date due to you to meet FDA/CTEP's reporting requirements (refer to designated time frame above for the due date), and forward the form along with the document on the next page to the facility/provider. After receiving the requested information from the medical records department and/or outside facility/provider, remove the patient name and identifiers listed on this page. Write the patient ID and AdEERS Ticket Number on each page being forwarded to CTEP. **Fax the requested information to: 301-230-0159.**

For additional guidance on disclosures of PHI for public health purposes to a government agency that also conducts research, see HIPAA Privacy Rule and Public Health: Guidance from CDC and the U.S. Department of Health and Human Services, located at http://www.cdc.gov/mmwr/preview/mmwrhtml/su5201a1.htm**.**

For assistance, contact the AdEERSMD Help Desk: **Email: AdEERSMD@tech-res.com**
Phone: 301-897-7497

Thank You for Your Timely Assistance in this Vital Research Effort!

Obtaining Medical Information from Outside Health Care Facilities for Patients on Clinical Studies

When Authorization for Protected Health Information (PHI) is NOT Required

[45 CFR Part 164.512(b)]

Information for the Clinical Investigator or Medical Records Department

Please note that this section pertains to both living and deceased persons.

Many Cancer Therapy Evaluation Program (CTEP) clinical sites have reported difficulty obtaining necessary patient medical records when the patient is seen/treated in an outside medical facility stating that HIPAA Privacy Rules prevent them from disclosing any Protected Health Information (PHI). The HIPAA Privacy Rule is not intended to impede public health activities. The HIPAA Privacy Rule permits certain disclosures of PHI for public health activities and research without a patient's authorization. Disclosures to clinical research facilities/clinical investigators in NCI sponsored clinical studies are permitted, as long as the reason for the requests fit within the Privacy Rule's relevant exception(s).

The disclosure of PHI is permitted under section 45 CFR Part 164.512(b) (1). If an entity qualifies as a public health authority, a covered entity may disclose PHI to the public health authority if the law authorizes the public health authority to collect or receive such information for the purposes set forth in section 45 CFR Part 164.512(b)(1).

There is a special procedure for disclosing PHI of deceased persons to a public health authority.

Please see below:

Accessing Information on Deceased Persons (Section 164.512)

A covered entity may disclose PHI of a deceased person to a clinical investigator, without the authorization of the deceased person's estate, if the clinical investigator provides the covered entity certain assurances**.** For this information, the clinical investigator **must provide documentation** that the person is deceased **and must submit** a request to the outside med facility stating that:

- the use/disclosure of the PHI is for research purposes only
- the information is necessary for research purposes
- the person is deceased

For additional guidance on disclosures of PHI for public health purposes to a government agency that also conducts research, see HIPAA Privacy Rule and Public Health: Guidance from CDC and the U.S. Department of Health and Human Services, located at:

http://www.cdc.gov/mmwr/preview/mmwrhtml/su5201a1.htm

Request for Information on Patient Participating in a NCI Clinical Research Study

The following patient is/was a participant in a Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnostics (DCTD), National Cancer Institute (NCI), clinical research study. As such, CTEP is required to meet Food and Drug Administration (FDA) established timelines when reporting adverse events from CTEP/DCTD/NCI-sponsored clinical research trials to the FDA and is requesting additional medical documentation/records regarding the adverse event(s)/toxicity(ies) and/or emergency room visit(s)/hospitalization(s) below. Please assist this process by:

- **sending the information below to the attention of: _____**
  Requestor name
- **contacting the requestor for any questions at: _____**
  Requestor contact number
- **forwarding the requested information listed below:**
  _____
  _____
  _____
  _____
- **writing the following information** on **each page** that is faxed to **_____:**
  Fax number

  Patient ID: _____
  Adverse Event(s)/Toxicity(ies): _____
  Emergency Room Visit Date(s): _____
  Hospitalization Date(s): _____
- **by the designated time frame: _____**

For assistance, contact the AdEERSMD Help Desk : **Email:** AdEERSMD@tech-res.com
Phone: **301-897-7497**

Thank You for Your Timely Assistance in this Vital Research Effort!