NCI GUIDELINES FOR INVESTIGATORS:

ADVERSE EVENT REPORTING REQUIREMENTS FOR DCTD (CTEP AND CIP) INDs AND IDEs

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1 Introduction

The Federal Food and Drug Administration (FDA), Department of Health and Human Services (DHHS), 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) and 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 (NCI), 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 are 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 clinical trials network programs as well as studies sponsored by the CIP. Adverse Event (AE) and Serious Adverse Event (SAE) reporting procedures as defined in the study protocol will always supersede the reporting procedures in the NCI AE Guidelines.

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

1.2 Purpose

- 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 and CIP as IND/IDE sponsors.
- Explain the role of the Cancer Therapy Evaluation Program-Adverse Events Reporting System (CTEP-AERS).

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 prior to reporting to relevant NCI staff for review.
- 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 suspension of the investigator.
- Investigators **MUST** immediately report to the sponsor any AE that is serious (see section 2.1.22 for definition of SAE) (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 AEs or risks with respect to the drug/device (21 CFR 312.50, 21 CFR 812).
- It is the responsibility of the sponsor to determine attribution for SAEs with respect to the drug/device.
- 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), of:
    - Any suspected adverse reaction that is both serious and unexpected.
    - Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
    - Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND/IDE and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the investigational agent.
    - Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

  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 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'). (The International Council for Harmonization [ICH] E2A, E6)

2.1.2. Attribution: An assessment of the relationship between the AE and the medical 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 CTEP-AERS are considered to have a suspected 'reasonable causal relationship' to the investigational agent/intervention. (ICH E2A)

For assistance, please contact AEMD@tech-res.com.

2.1.3. CAEPR: The Comprehensive Adverse Events and Potential Risks List (CAEPR) is an NCI-generated list of reported and/or potential AEs associated with an investigational agent currently under an NCI IND/IDE. Information contained in the CAEPR is compiled from the Investigator's Brochure (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 and AEs submitted through CTEP-AERS.

2.1.4. Cancer Therapy Evaluation Program-Adverse Event Reporting System (CTEP-AERS): A tool supporting regulatory and protocol compliance for adverse event reporting that allows local collection, management, and querying of AE data. This tool also supports service-based integration of data from Medidata Rave.

2.1.5. Cancer Trials Support Unit (CTSU): The CTSU is a service of the NCI designed to facilitate access to NCI-funded clinical trials for qualified clinical sites and to support the management and conduct of those clinical trials.

2.1.6. Clinical Data Update System (CDUS) is a legacy data collection method/system. For legacy studies assigned CDUS reporting, please refer to the CDUS Instructions and Guidelines for reporting requirements: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/cdus_ig_3r5_1.pdf.

2.1.7. 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 a commercially available agent is being used as an investigational agent for that particular protocol.

2.1.8. 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.

2.1.9. Clinical Trials Monitoring System (CTMS) The CTMS is a service of the NCI designed 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.

2.1.10. Data Mapping Utility (DMU): The DMU is a mapping tool through which required clinical trial data is transmitted to CTEP. DMU Reporting requirements can be found at: https://ctep.cancer.gov/protocolDevelopment/dmu.htm.

2.1.11. 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). Expectedness is determined by the Sponsor upon review of the Investigator Brochure and other relevant information. NCI/CTEP collates the AE information and provides it to NCI investigators in the CAEPR, SPEER and CRL. 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 (*e.g.*, IB for investigational agent).

2.1.12. Expedited Reporting: Investigators should report expected and unexpected SAEs based on the protocol requirements. Requirements for devices may differ and the protocol should be followed in such cases. Attribution, the relationship between the AE and causality by the study agent, should be provided by the investigator. Based on recent guidance, the final determination of attribution will reside with the Sponsor, in this case the NCI/CTEP. To ensure compliance with CFR regulations/guidances, as IND/IDE sponsor, NCI/CTEP requires that SAEs be submitted according to the timeframes in the AE reporting table assigned to the protocol (*i.e.*, Appendix 1 for NCI investigational agents/devices and Appendix 2 for CIP commercial agents). These AEs are to be submitted to NCI/CTEP via CTEP-AERS (see Section 4.0).

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

2.1.14. 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. (*e.g.*, a hospital visit where a patient is admitted for observation or minor treatment such as 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.

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

2.1.16. Investigational Device Exemption (IDE): An **IDE** allows the investigational device 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 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.

2.1.17. Investigational New Drug: Refers to any investigational agent that is used in a clinical investigation. It is 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)

2.1.18. Principal Investigator: A physician designated by the NCI grant/contract-funded institution or NCI CCR, who has organizational and fiscal responsibility for the use of federal funds to conduct a clinical study. This individual is responsible for conducting the clinical investigation at all sites (*i.e.*, under whose immediate direction the investigational agent/intervention is administered or dispensed to a subject).

2.1.19. Investigator: In the event an investigation is conducted by a team of individuals at a site, the investigator is any physician who assumes full responsibility for the treatment and evaluation of patients on research protocols as well as the integrity of the research data and is considered the responsible leader of the team at their site. (21 CFR 312.3)

2.1.20. 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)

2.1.21. Life-Threatening Adverse Event: Any SAE 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 SAE that, had it occurred in a more severe form, might have caused death. (FDA 21 CFR 312.32, ICH E2A)

2.1.22. Medical Dictionary for Regulatory Activities (MedDRA): A clinically validated international medical terminology used by regulatory authorities and the regulated biopharmaceutical industry throughout the entire regulatory process.

2.1.23. Medidata RAVE: The clinical data management system utilized across CTEP for the entry and management of clinical data for several NCI networks.

2.1.24. MedWatch: The FDA'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).

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

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

2.1.27. 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.

2.1.28. Serious Adverse Event (SAE): Any adverse drug event (experience) occurring at any dose that 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)

NOTE: SAE and expedited AE are used interchangeably in this document.

2.1.29. Source Document Portal (SDP): A tool that supports the upload of participant documents from an Electronic Health Record (EHR) or from a paper-based chart or report. All participant documents must have personally identifiable information (PII) removed. The SDP supports redaction of PII during the upload process.

2.1.30. Specific Protocol Exceptions to Expedited Reporting (SPEER): A subset of AEs within the CAEPR that contains a list of events that are protocol-specific exceptions to expedited reporting (See Section 2.3 for CAEPR information). AEs listed on the SPEER should be reported expeditiously by investigators to the NCI via CTEP-AERS **ONLY IF** they exceed the grade of the event listed in parentheses after the event. If the SPEER is part of a study that uses multiple investigational agents and the same AE is listed on the multiple SPEERs, use the lower of the grades to determine if expedited reporting is required. The SPEER is only used for investigational agents in CTEP IND studies.

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

2.1.32. Suspected Unexpected Serious Adverse Reaction (SUSAR): An adverse event that occurs in a clinical trial participant, which is assessed by the sponsor as being unexpected, unexpected, serious (See 21 CFR 312.32), and for which there is a reasonable possibility that the drug caused the adverse event (calls for 7-day or 15-day reporting to the FDA based on whether it is fatal/life-threatening or non-fatal/non-life-threatening).

2.1.33. Unexpected Adverse Event: An adverse event that is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed or is not consistent with the risk information described in the Investigator Brochure, CAEPR, SPEER, and/or CRL.

2.1.34. 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 Institutional review Board (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 an instrument 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 attribution require documentation by medical personnel who are directly involved in the clinical care of study participants.

Each CTCAE term 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 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 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.

NOTES:

- 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 CAEPR

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, and SAEs submitted through CTEP-AERS. The CAEPR and the Condensed Risk List (CRL), derived from the CAEPR, are meant to be used by investigators to prepare their Informed Consent Document (ICD). The safety profile for an investigational agent is reviewed at least annually in accordance with current Good Clinical Practice (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. CAEPRs and all CAEPR revisions are reviewed and approved by CTEP or CIP, and then by CTEP pharmaceutical collaborators.

2.3.1 Studies Requiring the Inclusion of a CAEPR:

NCI/CTEP requires the inclusion of a CAEPR (with SPEER when applicable) in studies described below.

- All studies conducted under an NCI/CTEP IND reviewed by CTEP or CIP that includes investigational agents/interventions for which NCI has a CAEPR.
- For studies not conducted under an NCI/CTEP IND but include agents for which NCI/CTEP has a CAEPR, the NCI CAEPR should be utilized but the SPEER must be removed.

2.3.2 As the CAEPR is revised, the SPEER is also reviewed and revised if needed, and the approved revisions will be sent to all Principal and other Investigators registered to NCI-approved studies using the agent(s). The letters below accompany the finalized CAEPR, and they inform sites conducting trials using the investigational agent that CTEP is requesting they revise their protocols and ICDs to include the revised CAEPR and Risk Profile, respectively.

- Request for Revision (RR) – Applies to protocols that are in review but have not been activated. A letter requesting a protocol revision due to certain changes including, but not limited to, updates to the CAEPR, CRL, and pharmaceutical section of the protocol, etc. with the next protocol submission to CTEP. This letter does not have a specified timeframe.

- Request for Amendment (RA) – Applies to protocols that have been activated. A letter requesting a protocol amendment due to certain changes including, but not limited to updates to the CAEPR, CRL, and pharmaceutical section of the protocol, etc. The response timelines can vary depending on the intent of the letter. The nature of the CAEPR changes do not result in any additions to the Risk Profile (ex. a change in frequency from “less likely” to “likely” for an AE that was already on the CAEPR or added risks that are very similar to risks already included in the previous version of the CAEPR and would have been communicated to patients in the informed consent document (ICD)). The sites have 45 calendar days for amendment submission.

- Request for Rapid Amendment (RRA) – Applies to protocols that have been activated. A letter requesting a protocol amendment due to updates to the CAEPR and CRL. The sites have 21 calendar days to submit their amendments to CTEP. After the 21 calendar days, the sites have 14 days to finalize the approval process and then the Type 2 AL is sent out (35 calendar days for amendment submission). CAEPR changes resulting in one of several items: (1) additions to the Risk Profile, but the change results in only a minimal to minor impact on the risk: benefit to the patient, or (2) other items such as new safety language or new required tests. (Examples include a new AE that was not previously on the CAEPR, an increase in frequency of an AE, or a change in risk from one category to another which would not halt accrual because that risk was less than a certain percentage).

- Action Letter (AL) – Applies to protocols that have been activated. A letter sent to the sites requiring some action to be taken based on changes to the risk profile.
  - Type 1 AL- Rarely used. A CAEPR change resulting in substantive change (for the worse) on the patient’s risk: benefit balance. Therefore, the action required is immediate suspension of new accrual to trials using the agent. This type of AL is not preceded by an RRA.
  - Type 2 AL- Commonly used. A letter sent to sites after an RRA letter has been issued requiring a protocol amendment to include the new CAEPR and

CRL. Sites that do not respond to the initial RRA will risk being temporarily closed to accrual and will have 14 calendar days to submit an amendment to CTEP or risk having the study permanently closed and the study PI suspended.

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. 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]) Appendices 4 (HIPAA Cover Memo) and 5 (HIPPA Document may be helpful when requesting supporting medical documents for participants treated in institutions outside of the institution conducting the clinical trial.

3 Routine AE Reporting to NCI

3.1 Requirements

3.1.1 Routine AE reporting requirements vary based on study phase, randomization status, agent type (investigational, commercial), IND status/holder, etc. and are defined by the assigned monitoring method for each protocol.

3.2 Monitoring Method

3.2.1 The monitoring method defines what clinical data NCI requires for the clinical trial and on what schedule. Further information on monitoring methods can be found on the CTEP Website at https://ctep.cancer.gov/protocolDevelopment/cde_data_policies.htm.

3.2.2 Routine AE reporting is required for the following monitoring methods:

3.2.2.1 DMU Complete (see link above)

3.2.2.2 DMU Light (see link above)

3.2.2.3 CTMS (see link above)

3.2.2.4 CDUS Complete (legacy) (see link above)

3.3 CTEP Medical Officer Review

Routine AE data obtained from the aforementioned data monitoring methods during the conduct of a study will be reviewed monthly by CTEP Medical Officers.

4 Expedited AE Reporting to NCI

4.1 CTEP-AERS

CTEP-AERS allows expedited reporting of SAEs to NCI for all studies including those not under an NCI IND/IDE, commercial agent-only, investigational agent/intervention and commercial agent on separate arms, investigational agent/intervention and commercial agent on the same arm, or studies only using radiation (diagnostic or therapeutic), devices, surgical or behavioral interventions, or any combination of the preceding.

PLEASE NOTE: Expedited reports submitted 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. Moreover, if CTEP is distributing the investigational agent, then copies of all IND Safety Reports submitted by the non-CTEP IND sponsor to the FDA should be forwarded to CTEPSupportAE@tech-res.com for our reference.

Expedited reporting requirement tables for NCI IND/IDE studies as well as CIP studies can be found in Appendices 1 and 2. The tables for NCI IND/IDE studies as well as CIP studies represent investigator reporting requirements in compliance with 21 CFR 312.64, as amended on March 28, 2011.

An SAE report for all studies utilizing agents under an NCI IND/IDE must be submitted electronically to NCI via CTEP-AERS. The link to CTEP-AERS can be found on the CTEP website: https://ctep.cancer.gov/.

4.2 Medical Documentation

Any medical documentation supporting an expedited report (*e.g.*, H & P, admission and/or progress notes, consultations, lab results, etc.) **should** be provided at the time an SAE is submitted to CTEP-AERS but **MUST** be uploaded within 24-48 hours via the Source Document Portal (SDP), accessed via CTEP-AERS.

NOTE: Submission of supporting medical information for non-NCI IND/IDE studies should be submitted to the Lead Organization for the study or per protocol requirements.

NOTE: English is required for all supporting documentation. It is the responsibility of the investigator or the Lead Organization coordinating office to obtain translation of supporting medical information submitted to NCI.

4.3 Expedited AE (i.e., SAE) Reporting Timelines

Appendices 1 and 2 detail the expedited reporting requirements for AEs that occur on trials utilizing an agent under an NCI IND/IDE or CIP Studies Using Commercial Imaging Agent(s). The report type/timelines are defined below:

- 24-Hour; 5 Calendar Day
  - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the event, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. **This is a 2-step process.**
- 24-Hour; 10 Calendar Day
  - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the event. A complete expedited report on the SAE must be submitted within 10 calendar days of the investigator learning of the event.

- 15 Calendar Day
  - A complete expedited report on the SAE must be submitted within 15 calendar days of the investigator learning of the event.

4.4 24-hour Notification/5-Day Reports for NCI IND/IDE Trials and non-NCI IND/IDE Trials

The SAE 24-hour notification requirement provides an early detection system for potential safety problems.

THIS IS A TWO-STEP PROCESS. A 24-hour notification **MUST** be followed by a complete report within 5 calendar days of the 24-hour notification or the entire report will be withdrawn.

4.4.1 To fulfill the 24-hour reporting requirement, SAEs must be reported electronically via CTEP-AERS within 24 hours of learning of the event. Subsequently, a complete report must be submitted within the following 5 days.

4.4.2 To ensure vigilance for SAEs that require 24-hour notification, CTEP-AERS is programmed to facilitate complete, timely submission. Initiation of a CTEP-AERS 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, local treating physician, Study PI, and Lead Organization AE 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, local treating physician, Study PI, and Lead Organization's Adverse Event Coordinators (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, the incomplete 5-day report **AND** the 24-hour notification will be flagged by the system as 'Initiated, not submitted' and will no longer be accessible by the investigator/site. A final email is sent to the Reporter, local treating physician, Study PI, Lead Organization's Adverse Event Coordinators (where applicable) and to NCI notifying all that the report has been withdrawn. Personal correspondence from NCI will follow. Although no longer accessible by the investigator/site, 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.

4.5 24-hour Notification/10-Day Reports for NCI IND/IDE Trials and non-NCI IND/IDE Trials

The SAE 24-hour notification requirement provides an early detection system for potential safety problems.

THIS IS A TWO-STEP PROCESS. A 24-hour notification **MUST** be followed by a complete report within 10 calendar days of the 24-hour notification or the entire report will be withdrawn.

4.5.1 To fulfill the 24-hour reporting requirement, SAEs must be reported electronically via CTEP-AERS within 24 hours of learning of the event. Subsequently, a complete report must be submitted within the following 10 days.

4.5.2 To ensure vigilance for SAEs that require 24-hour notification, CTEP-AERS is programmed to facilitate complete, timely submission. Initiation of a CTEP-AERS 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 10 calendar days of the 24-hour notification.

3. On calendar day 5, if the complete report has not been submitted, a system-generated email is sent to the Reporter, local treating physician, Study PI, and Lead Organization AE Coordinator (where applicable). The message is a reminder that the complete report associated with a 24-hour notification is due in 5 more calendar days.

4. On calendar day 11, if the complete report has not been submitted, the incomplete 10-day report **AND** the 24-hour notification will be flagged by the system as 'Initiated, not submitted' and will no longer be accessible by the investigator/site. A final email is sent to the Reporter, local treating physician, Study PI, Lead Organization's Adverse Event Coordinators (where applicable) and to NCI notifying all that the report has been withdrawn. Personal correspondence from NCI will follow. Although no longer accessible by the investigator/site, it is available for audit purposes.

5. 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 an internet connection.

4.6 SAE Reporting of Hospitalization or Prolongation of Hospitalization for all Phases of Trials

NCI defines hospitalization for SAE 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 SAE 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 SAE, and therefore is not to be reported either as a routine AE or SAE.

4.7 Important Medical Events (IME)

Any event that results in a persistent or significant incapacity/substantial disruption of the ability to conduct normal life functions, or congenital anomaly/birth defect, or is an IME, which based upon the medical judgment of the investigator may jeopardize the participant and require intervention to prevent an SAE, must be reported via CTEP-AERS if the event occurs following investigational agent administration.

4.8 Expedited Reporting via the Rave/CTEP-AERS Integration

For studies utilizing the Rave/CTEP-AERS Integration, all adverse events must be first entered in Rave. CTEP-AERS will not allow an expedited report to be initiated directly in CTEP-AERS; the Reporter must start in Rave.

After entering the Adverse Event in the Rave Adverse Event CRF, the Reporter should then run the Rules Engine call (RE Call) via the *Expedited Reporting Evaluation* form in Rave. The CTEP-AERS reporting recommendation will be displayed in Rave. If an expedited report is recommended and the Reporter is in agreement with the recommendation, then the Reporter clicks the hyperlink to move to CTEP-AERS and complete the report in the required timeframe.

An Expedited Safety Reporting Rules User Guide is available electronically on the CTSU website: Resources tab → CTSU Operation Information → User Guides & Help Topics.

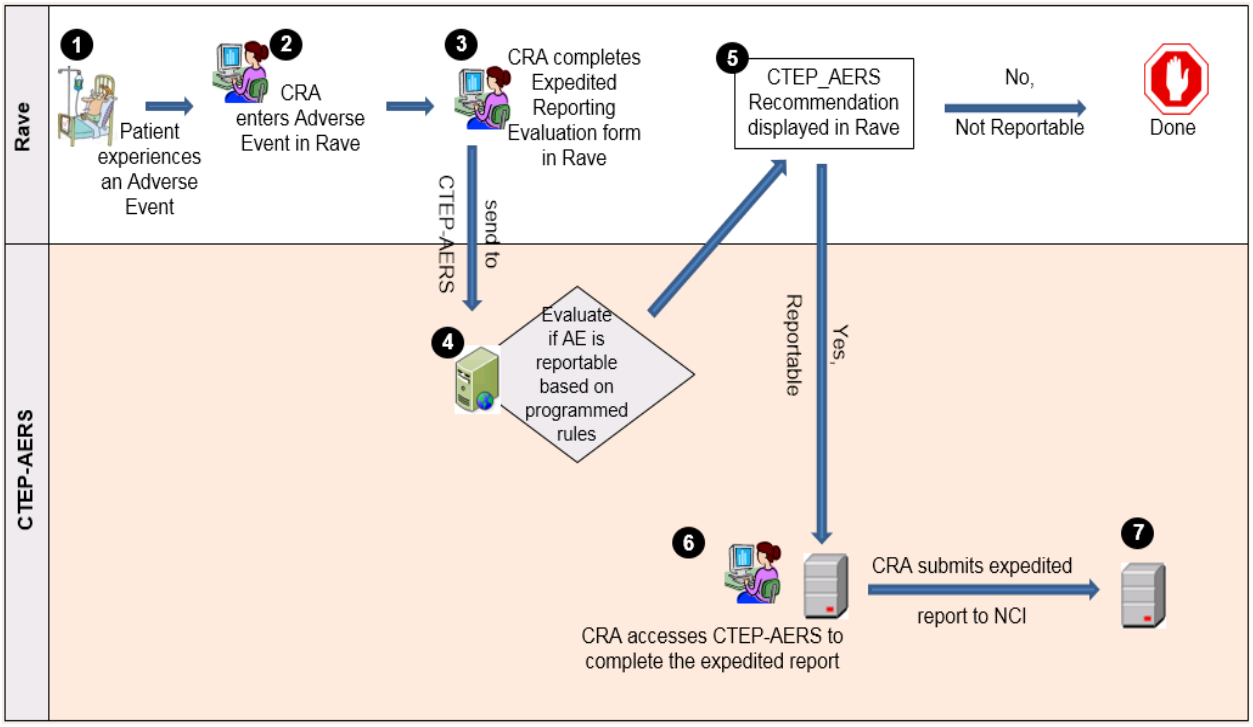


Figure 1. Workflow of Integration Between Medidata RAVE and CTEP-AERS.

4.9 Resources/Contact Information

- Adverse Event and CTEP-AERS Medical Questions/Help:
  email: AEMD@tech-res.com, *phone:* (301) 897-7497,
- Technical Questions/Help (e.g., IT issues, system problems, etc.):
  email: ctephelpdesk@nih.gov, *phone:* 1-888-283-7457 or 301-840-8202
- CTEP-AERS Frequently Asked Questions (FAQ):
  https://ctepcore.nci.nih.gov/ctepaers/help/webhelp/welcome/help%20-%20frequently%20asked%20questions.htm
- CTEP-AERS Training: Training resources can be found here:
  https://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm

5 Reporting Requirements for Specialized AEs

5.1 Pre-existing Conditions (formerly referred to as Baseline AEs)

A pre-existing medical condition identified on baseline assessment is not considered an AE and should not be reported as a routine or expedited AE. 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 (refer to Appendices 1 and 2). Whether or not an expedited report is required, the worsened event should be reported as a routine AE.
2. If the AE resolves and then recurs, the investigator must re-assess the event to determine if an expedited report is required (refer to Appendices 1 and 2). Whether or not an expedited report is required, the recurrent event should be reported as a routine AE.

For example: In a clinical situation when a participant enters a study utilizing an agent under a CTEP IND/IDE with Dyspnea equivalent to CTCAE grade 1.

ROUTINE reporting of grade 1 Dyspnea is not required. If it increases in grade, it should be reported as a routine AE and evaluated for expedited reporting.

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

- If the Dyspnea remains unchanged while on study, a CTEP-AERS report is **NOT** required.
- If at any time on study the Dyspnea results in hospitalization and/or prolongation of hospitalization, a CTEP-AERS report is required regardless of grade, expectedness and attribution (unless the AE is listed on the SPEER at or above the grade experienced by the participant).
- If at any time while on study the Dyspnea value increases in grade and meets seriousness criteria, an expedited report is required (unless the AE is listed on the SPEER at or above the grade experienced by the participant).
- If the investigator determines that the Dyspnea is expected as defined by the protocol, at or below the grade listed on the SPEER, an expedited report is **NOT** required.

5.2 Pre-Treatment AEs

A pre-treatment adverse event is an adverse event that occurs after a participant has signed an informed consent, but before intervention has begun. Refer to the protocol document to determine routine and/or expedited reporting requirements.

5.3 Persistent/Recurrent AEs

5.3.1 Persistent AE

A persistent AE (e.g., chronic) is one that extends continuously, without resolution between treatment cycles/courses.

Instructions for **ROUTINE** reporting:

- For legacy studies utilizing CDUS Complete monitoring, the AE must be reported only once unless the grade becomes more severe in a

subsequent course. If the grade becomes more severe in a subsequent course, the AE must be reported again with the new grade.

- For Rave studies utilizing DMU Light or DMU Complete, the persistent (ongoing) AE will be copied forward each cycle until an end date is recorded. If the grade becomes more severe on a subsequent course, the original AE must have an end date entered on the original course and the higher-grade AE entered as a new AE in Rave on the subsequent course. NCI will receive these AEs with each DMU data submission. There may be some variation depending on a study's Rave configuration.
- For non-Rave studies utilizing DMU Light or DMU Complete, 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 in the subsequent course.

Instructions for **EXPEDITED** reporting:

- If the AE meets Expedited reporting requirements (See Appendices 1 and 2), it should be reported only once unless the grade becomes more severe in the same (submit an amendment to the original expedited report) or a subsequent course (submit a new expedited report associated with the subsequent course).

5.3.2 Recurrent AEs

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

Instructions for **ROUTINE** reporting: An AE that resolves and then recurs during a subsequent cycle/course must be reported in each cycle on which it occurs.

Instructions for **EXPEDITED** reporting: An AE that resolves and then recurs during a subsequent cycle/course does not require CTEP-AERS reporting unless:

1) The grade increases **OR**
2) Hospitalization or prolongation of hospitalization (≥24 hours) at any time is associated with the recurring SAE, even if the grade does not increase.

Example of expedited reporting requirements of the AE 'Platelet count decreased' when hospitalization is **NOT** associated with the Platelet count:

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Platelet count decreased	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L	-

Baseline	Platelet count = 200,000
Cycle 1	• Platelet count decreases to 40,000 = grade 3 ○ An expedited report IS required. • Platelet count increases to 50,000 by end of Cycle 1.
Cycle 2	• Platelet count 50,000 = grade 2 (persistent AE) ○ An expedited report is NOT required. • Platelet count resolved to within normal limits at end of Cycle 2.
Cycle 3	• Platelet count decreases to 24,000 = grade 4 (recurrent AE with increased grade) ○ An expedited report IS required. • Platelet count increases to 76,000 (grade 1) at end of Cycle 3.

Cycle 4	• Platelet count decreases to 24,000 = grade 4 (recurrent AE with same grade)
	  ○ Expedited reporting is NOT required.
	• Platelet count decreases to 24,000 = grade 4 (recurrent AE with same grade) but hospitalization occurs
	  ○ Expedited reporting IS required.

IMPORTANT: An event becomes an SAE and requires expedited reporting for any AE resulting in hospitalization or prolongation of hospitalization (≥24 hours) at any time, regardless of persistent/recurring AEs.

5.4 AEs Experienced Utilizing Investigational Agent(s) and Commercial Agent(s) on SEPARATE Arms

Routine Reporting

- Routine AE reporting for all clinical studies using an investigational agent/intervention and a commercial agent on separate arms must be reported as specified in the protocol.

Expedited Reporting

- An SAE that occurs on an arm using an investigational agent /intervention under an IND/IDE must be assessed in accordance with the guidelines as specified in the protocol, and where indicated, an expedited report must be submitted. In general, for investigational agents this aligns with Appendix 1 for CTEP agents and Appendix 2 for CIP commercial agents.

- An SAE that occurs on an arm using a commercial agent on a separate treatment arm must be assessed as specified in the protocol. **Refer to each protocol for specific SAE reporting requirements or exceptions.**
- **NOTE**: CTEP-AERS is programmed to automatically submit the reports for grade 1-4 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.

5.5 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm

Routine Reporting

- Routine AE reporting for all clinical studies using an investigational agent /intervention in combination with a commercial agent must be reported as specified in the protocol.

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 routine reporting.

Expedited Reporting

- An SAE 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 SAE that occurs prior to administration of the investigational agent/intervention, but after administration of the commercial agent, must be assessed as specified in the protocol. **Refer to each protocol for specific SAE reporting requirements or exceptions.**
    - **NOTE**: CTEP-AERS is programmed to automatically submit the reports for grade 1-4 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.
- An investigational agent/intervention might exacerbate the expected SAEs associated with a commercial agent. Therefore, if an expected SAE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

5.6 Guidance for Specific Examples for Expedited Reporting

5.6.1 Protocol-Specific Exceptions

The expedited reporting requirements described below supersede the NCI tables found in Appendix 1. Routine AE reporting to NCI, however, remains unchanged.

- SPEER (subcategory within the NCI Agent-Specific CAEPR): An SAE, occurring at a grade no greater than that listed in the SPEER, does not need expedited reporting to CTEP, as it is included in the IB and/or is well-documented in our IND safety experience. If the SPEER is part of a study that uses multiple investigational agents and the same SAE is listed within

multiple SPEERs, use the lower of the grades listed to determine if expedited reporting is required.

- Additional AE Inclusions or Exclusions: Protocol-specific exceptions to the expedited reporting tables may be provided by the research site, NCI, and/or the pharma partner. Specific inclusions may be AESIs (see below). Exclusions are most often disease-specific events common to the study population. However, if an aggregate analysis indicates that they are occurring more frequently or at higher severity in the drug treatment group than a control group, then an expedited report should be submitted at that time. The safety team or an independent group should monitor these rates at appropriate intervals.

- Adverse Events of Special Interest ("AESI") are in some instances listed in the "Expedited Adverse Event Reporting" section of the protocol. These are explicit events that require rapid reporting for real-time monitoring by the sponsor, even though they might not be considered serious. Examples include events of scientific or medical concern that might be potential precursors or portents of more serious medical conditions. Although they are to be reported via CTEP-AERS to facilitate real-time review, AESIs would only be classified as SAEs if the investigator or sponsor determined that they met the regulatory criteria for serious events. When CTEP is the IND Sponsor, AESIs are agreed upon by both CTEP and their pharma collaborator. When an SAE is listed both on the SPEER and in the list of protocol specific AESIs, the AESI takes precedence over the SAE listed on the SPEER and should be reported to CTEP.

5.6.2 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects, is considered to be an SAE and must be reported via CTEP-AERS if they occur at any time following treatment with an agent under a NCI IND/IDE since they are considered to be a SAE (see Section 2.1.22) and must be reported to the sponsor as specified in 21 CFR 312.64(b).

5.6.3 Death

Reportable Categories of Death

- Death attributable to a CTCAE term (i.e., any grade 5 in the CTCAE.)
- Sudden Death NOS: An unexpected death that cannot be attributed to a CTCAE term associated with Grade 5.

- Death NOS: Death that cannot be attributed to a CTCAE term associated with Grade 5.

- Death due to Disease progression: Death due to disease progression that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to Disease progression should be reported as Grade 5 Disease progression. Evidence that the death was a manifestation of

underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

- Death Neonatal: Newborn death occurring during the first 28 days after birth.

- Pregnancy loss: Death in utero.

NOTE: Any death occurring ***within 30 days*** of the last dose, regardless of attribution to the investigational agent/intervention, requires expedited reporting within 24 hours.

NOTE: Any death occurring ***greater than 30 days*** after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours **only if** it is possibly, probably, or definitely related to the investigational agent/intervention.

5.6.4 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 occurring at any time following treatment with an agent under an NCI/CTEP IND/IDE to be reported via CTEP-AERS. The definitions provided are the CTCAE definitions. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (*e.g.*, Acute Myelocytic Leukemia [AML]). Definition: A disorder characterized by leukemia arising as a result of mutagenic effect of chemotherapy agents.
  - Myelodysplastic syndrome (MDS). Definition: A disorder characterized by insufficiently healthy hematopoietic cell production by the bone marrow.
  - Treatment-related secondary malignancy. Definition: A disorder characterized by development of a malignancy most probably as a result of treatment for a previously existing malignancy.
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

5.6.5 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.

5.6.6 Pregnancy, Pregnancy Loss, and Death Neonatal

NOTE: When submitting CTEP-AERS reports for “Pregnancy”, “Pregnancy loss”, or “Death neonatal”, the CTEP Clinical Trial Pregnancy Information Form (Feb 2021) should also be completed for participants who became pregnant during the study within 24-48 hours of the time the investigator

becomes aware of the pregnancy and uploaded along with any additional medical information to SDP. This excludes any pregnancy initiated 12 months after the study participant's last dose of investigational agent. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The CTEP Clinical Trial Pregnancy Information Form (July 2024) can be accessed at: https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm.

5.6.6.1 Pregnancy

- Although not an AE in and of itself, pregnancy as well as its outcome must be documented via CTEP-AERS. CTEP agrees to soliciting information about pregnancy outcomes only from the study participant without approaching the partner for consent. The investigator will make best efforts to collect the de-identified information as outlined in the CTEP Clinical Trial Pregnancy Information Form (July 2024) only from the study participant via the study site.

- Because participants who become pregnant during the study risk intrauterine exposure of the fetus to agents which may be teratogenic, NCI is requesting that pregnancy be reported in an expedited manner via CTEP-AERS within 24-48 hours of awareness as Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)" under the Pregnancy, puerperium and perinatal conditions SOC.

- In the event a male Study participant impregnates a non-participant female, NCI is requesting that pregnancy be reported in an expedited manner via CTEP-AERS within 24-48 hours of awareness as Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)" under the Pregnancy, puerperium and perinatal conditions SOC.

- The pregnancy outcome for participants on-study should be reported via CTEP-AERS as an amendment to the previous report within 24-48 hours of the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report. Please see the note above (Section 5.6.6) for how to submit the form.

- CTEP agrees to consent only the study participants and not the pregnant partner for reporting pregnancy and pregnancy outcome. Only when an investigator is made aware of any pregnancy occurring in a patient or patient's partner from the time of consent to 90 days after the last dose of the study drug, should it be reported and then followed for outcome. Newborn infants should be followed until 30 days old.

5.6.6.2 Pregnancy loss

- Pregnancy loss is defined in CTCAE as "Death in utero."

- Pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss."

NOTE: Pregnancy loss should NOT be reported as a Grade 5 event using "Other, specify" or any other Grade 5 CTCAE term. If reported as such, CTEP-AERS interprets this as a death of the participant being treated.

5.6.6.3 Neonatal Death

- Death neonatal is defined in CTCAE as "Newborn death occurring during the first 28 days after birth." It is intended for use when the neonate is **NOT** the study participant. If the neonate **IS** the study participant, please select one of the other reportable categories of death.
- If a neonatal death is felt by the investigator to be at least possibly due to the investigational agent/intervention, it should be reported expeditiously as **Grade 4 "**Death neonatal."

  NOTE: Neonatal death should **NOT** be reported as a Grade 5 event using "Other, specify" or any other Grade 5 CTCAE term. If reported as such, CTEP-AERS interprets this as a death of the participant being treated. If the neonate **IS** the study participant, please select one of the other reportable categories of death.

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** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 calendar days	24-Hour notification, 5 calendar days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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.

Effective Date: August 30, 2024

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

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** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-2 Timeframes	Grade 3-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 3-5 SAEs
- Within 10 calendar days for Grade 1-2 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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.

Effective Date: August 30, 2024

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** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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.

Effective Date: August 30, 2024

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 Commercial Agent Studies: Expedited Reporting Requirements for Adverse Events that Occur in a CIP Non-IND/IDE trial 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** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening AE
3) An AE 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 SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.

[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 notifications are required for all SAEs followed by a complete report

- Within 5 calendar days for Grade 4-5 SAEs
- Within 10 calendar days for Grade 1-3 SAEs

[2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE 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.

Effective Date: August 30, 2024

Appendix 3: Contact Information for NCI Safety Reporting

CTEP-AERS website	https://ctepcore.nci.nih.gov/ctepaers/security/login
Adverse Events Helpdesk Phone for SAE reporting	301-897-7497 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
CIP SAE Help Phone for SAE reporting*	301-897-1704 Monday through Friday, 7:00 AM to 7:00 PM (US Eastern Time)
Source Document Portal (SDP) supporting Medical Documentation	The SDP is accessed from CTEP-AERS. Log in and find the report for which you want to upload supporting documentation. Use the "Actions" button to select "Upload/View Supporting Documents."
Adverse Events Medical Helpdesk Email	AEMD@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
CTEP-AERS Technical Help Email	ctephelpdesk@nih.gov
CTCAE term/Grade selection Help/Questions Email	AEMD@tech-res.com
CTEP Clinical Trial Pregnancy Information Form	https://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

*Office phone is accessible 24 hrs per day 7 days a week. The CTEP-AERS 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 Patient Health Information (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.

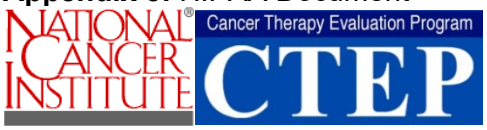
STEP 4: If the patient is deceased, please follow the instructions listed on page 2.

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 Adverse Events Medical Helpdesk by email: AEMD@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 submitted to the Source Document Portal.:

  Patient ID: _____

  Study number_____

  CTEP-AERS Report 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 image

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's name and identifiers listed on this page. Write the patient ID and CTEP-AERS Ticket Number on each page being forwarded to CTEP.

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.

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) and/or Cancer Imaging Program (CIP) 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.

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/email address
- **Submitting the requested additional information, as soon as possible, using the following method:**
  1. **Use the CTSU Source Document Portal (SDP).**
- **Writing the following information** on **each page** that is submitted**:**

  Patient ID: _____

  Study number:_____

  CTEP AERS Report number:_____

  Adverse Event(s)/Toxicity(ies): _____

  Emergency Room Visit Date(s): _____

  Hospitalization Date(s): _____
- **By the designated time frame:** _____

For assistance, contact the Adverse Events Medical Help Desk:
Email: AEMD@tech-res.com
Phone: 301-897-7497

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

Appendix 6: Example Comprehensive Adverse Events and Potential Risks list (CAEPR) for Investigational Agent (NSC #)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with ***bold*** and ***italicized*** text. This subset of AEs (SPEER) is a list of events that are protocol-specific exceptions to expedited reporting to NCI via CTEP-AERS (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 1141 patients.* Below is the CAEPR for oxaliplatin.

NOTE: Report AEs on the SPEER via CTEP-AERS **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.2

Adverse Events with Possible Relationship to Investigational Agent (CTCAE 4.0 Term) [n= 1141]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 4)***
	Disseminated intravascular coagulation		***Disseminated intravascular coagulation (Gr 4)***
	Febrile neutropenia		***Febrile neutropenia (Gr 4)***
	Hemolysis		***Hemolysis (Gr 1)***
CARDIAC DISORDERS			
	Atrial fibrillation		***Atrial fibrillation (Gr 4)***
	Atrial flutter		***Atrial flutter (Gr 1)***
	Paroxysmal atrial tachycardia		***Paroxysmal atrial tachycardia (Gr 2)***
	Sinus bradycardia		***Sinus bradycardia (Gr 3)***
	Sinus tachycardia		***Sinus tachycardia (Gr 3)***
	Supraventricular tachycardia		***Supraventricular tachycardia (Gr 4)***
	Ventricular arrhythmia		***Ventricular arrhythmia (Gr 4)***
	Ventricular fibrillation		***Ventricular fibrillation (Gr 4)***
	Ventricular tachycardia		***Ventricular tachycardia (Gr 2)***

Appendix 7: AE and SAE Reporting Algorithm
AE and SAE Reporting