HELPFUL DEFINITIONS/INFORMATION

Adverse Event (AE) is defined by the FDA and by NCI in *NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs*, as 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).

Serious Adverse Event (SAE) is defined by FDA and NCI as 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: death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization (for >24 hours), a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, a congenital anomaly/birth defect, or an Important Medical Event (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.

Hospitalization is defined as an inpatient stay equal to or greater than 24-Hours
[Does not Include Hospitalization for Observation or Minor Treatment and Release in less than 24-Hours or Hospitalization for PK Sampling.]

Baseline AE is a condition that exists at baseline. Baseline AEs are only reported if the condition increases in severity [grade increases] and/or results in hospitalization or prolongation of hospitalization. Baseline AEs must be re-assessed through the study.

Persistent AE is an AE that extends continuously, without resolution between treatment cycles/courses. The AE must be reported only once unless the grade becomes more severe in a subsequent course. It will then be reported with the new grade.

Recurrent AE is an AE that occurs and resolves during a cycle/course and then reoccurs in a later cycle/course. An AE that resolves and the recurs during a subsequent cycle/course will be reported if the grade increased OR hospitalization is associated with the recurring AE.

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 to be reported via CTEP-AERS.

Second Malignancy A cancer that is unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy. In general Second malignancies require **ONLY** routine reporting, however, there are a few protocols that require expedited reporting of a Second Malignancy as well. You should consult Section 16.1.

Reportable Categories of Death [CTCAE v5.0]

- Death - Utilizing an appropriate CTCAE term
- Sudden Death NOS
  [Defined as an unexpected death that cannot be attributed to a CTCAE term associated with Grade 5.]
- .Death NOS
  [Defined as death that cannot be attributed to a CTCAE term associated with a Grade 5.]
- Disease Progression
  [Defined as death due to disease progression that cannot be attributed to a CTCAE term associated with Grade 5]. Evidence that the death was a manifestation of the underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted as part of the supporting documentation.

*Note: For reporting a death due to disease progression in **CTCAE v4.0** report as Grade 5 **"Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name.
Evidence that the death was a manifestation of the underlying disease (e.g., radiological changes suggesting tumor growth or progression; clinical deterioration associated with a disease process) should be submitted.

When Amending a CTEP-AERS Report keep in mind **"One Cycle / One Ticket"**
You should amend an original CTEP-AERS report with information and/or additional events if this information is associated with the same cycle/course of treatment as indicated on the original CTEP-AERS report.

Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

Pregnancy: Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" SOC Pregnancy, puerperium and perinatal conditions CTCAE v5.0.

Pregnancy Loss: Pregnancy loss is defined in CTCAE v5.0 as "Death in utero." Pregnancy loss should be reported expeditiously as Grade 4 "Pregnancy loss" under SOC Pregnancy, puerperium and perinatal conditions.

Death Neonatal: "Death neonatal" is defined in CTCAE v5.0 as "Newborn death occurring during the first 28 days after birth. A neonatal death should be reported expeditiously as Grade 4 "Death Neonatal" SOC General disorders and administration site conditions.

Resources and Contact Information

General email: adr@swog.org

Kari Williams SWOG SAE Program Manager
Phone: 210-614-8808 extension 1020
Email: kwilliams@swog.org

Patti Felts SWOG SAE Coordinator
Phone: 210-614-8808 extension 1015
Email: pfelts@swog.org

For Information on CTEP-AERS application go to https://ctep.cancer.gov

- Click on Protocol Development
- Choose Adverse Event/CTCAE from the menu
- NCI Guidelines for Investigators: Adverse Event Reporting Requirements (September 16, 2013)
- SWOG Policy #23 available on SWOG website

CTEP-AERS **Medical** Questions / Help:

Email: aemd@tech-res.com

Phone: (301) 897-7497

Fax: (301) 897-7404

CTEP-AERS **Technical** Questions / Help:

Email: ncictephelp@ctep.nci.nih.gov

Phone: 1-888-283-7457 or 301-948-2242

The Following Guidance will be Included in Protocols Utilizing the Rave/CTEP-AERS Integration

Adverse Event Reporting Requirements

Please Note: This protocol utilizes Rave® / Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration for expedited reporting of serious adverse events. The CTEP-AERS integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. The Clinical Research Associate (CRA) will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free (fields
  added to the form during study build do not need to be query free for the integration call with CTEP-AERS to be a success).

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence, that Internet connectivity is lost; a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the deep link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and

- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

If you have questions about this process, please contact the SAE Program Manager 210-614-8808 or email adr@swog.org.

The CTEP-AERS electronic reporting system "Help" feature has detailed instructions in the section "Submitting Reports for RAVE Users".

There will also be an additional reminder leading into each expedited reporting table:

NOTE: For this study, all adverse events requiring expedited reporting must initially be reported on the Adverse Event Form in the appropriated Treatment Cycle folder in Medidata Rave. Once the adverse event is entered into RAVE, the Rules Engine will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Adverse Event Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Sites are encouraged to confirm the Expedited Reporting Evaluation Recommendation with the reporting criteria outlined in Table XX.X

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

MEMORANDUM

DATE: March 25, 2020

FROM: Meg Mooney, MD, Associate Director, CTEP, DCTD, NCI
Jeff Moscow, MD, Chief, IDB, CTEP, DCTD, NCI
S. Percy Ivy, MD, Program Director-ETCTN, Assoc. Chief, IDB, CTEP, DCTD, NCI
Worta McCaskill-Stevens, MD, Director, NCORP, DCP, NCI

TO: Principal Investigators and Site Staff Conducting NCI CTEP, CIP, and NCORP-Supported Clinical Trials

SUBJECT: Guidance for Collection of Adverse Events Related to COVID-19 Infection

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Infections occurring in subjects on clinical trials are considered adverse events and should be reported per protocol guidelines via normal procedures (on CRFs/Rave and via CTEP-AERS if serious).

Please document COVID-19 related adverse events as follows:

Infections and infestations - Other, specify
Specify = COVID-19

Additionally, please record (and if applicable, report via CTEP-AERS) any other Adverse Events the subject experiences such as Dyspnea, Acute respiratory distress syndrome, etc.

CTEP-AERS specific instructions:

- **Narrative**: Identify all pertinent facts related to the COVID-19 infection including, but not limited to the following:
  - Presumptive vs confirmed diagnosis. If presumptive, please update your narrative if/when diagnosis is confirmed, including timelines.
  - Treatment information
  - Recovery information, including timelines
  - Outcome information/status
- **Supporting documentation**: Please fax supporting documentation including admission notes, progress notes, clinical visits, and discharge summary if/when available.
  - Fax Number: 301-897-7404, include protocol number, ticket number and subject ID on the fax cover sheet and each page faxed.

Queries:

Medical Questions/Help:
Email: aemd@tech-res.com
Phone: (301) 897-7497
Fax Number: 301-897-7404

Technical CTEP-AERS Questions/Help:
Email: ncictephelp@ctep.nci.nih.gov
Phone: 1-888-283-7457

UAMS | University of Arkansas for Medical Sciences

Helpful Resources

- https://crawb.crab.org/txwb/CRA_MANUAL/Vol1/chapter%2013_Serious%20Adverse%20Events.pdf
- https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=312.32
- https://gcp.nidatraining.org/modules/4/pdf
- https://ccrod.cancer.gov/confluence/download/attachments/71041052/AE_UP6.pdf
- https://www.fda.gov/media/72267/download
- https://ccrod.cancer.gov/confluence/download/attachments/71041052/AE_UP6.pdf