SERIOUS ADVERSE EVENT REPORTING

ADVERSE EVENT

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

A new event which was not pre-existing at initial study drug administration
A pre-existing event which recurs with increased intensity or increased frequency subsequent to initial study drug administration
An event which is present at the time of study drug administration which is exacerbated following initial study drug administration
SERIOUS ADVERSE EVENT

- SAE’s are a sub-set of all adverse events collected
- The reporting of SAE’s is in addition to, and does not supplant, the necessity of adequately reporting adverse events on the data records and in the final results of the clinical trial.

SAE REPORTING

GRADE

GRADE 1  MILD
GRADE 2  MODERATE
GRADE 3  SEVERE
GRADE 4  LIFE-THREATENING
GRADE 5  FATAL
**ATTRIBUTION**

<table>
<thead>
<tr>
<th>RELATIONSHIP</th>
<th>ATTRIBUTION</th>
<th>DESCRIPTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unrelated to Investigational Agent / Intervention</td>
<td>Unrelated</td>
<td>The AE is clearly NOT Related to the intervention</td>
</tr>
<tr>
<td></td>
<td>Unlikely</td>
<td>The AE is Doubtfully Related to the intervention</td>
</tr>
<tr>
<td>Related to Investigation Agent / Intervention</td>
<td>Possible</td>
<td>The AE May be Related to the intervention</td>
</tr>
<tr>
<td></td>
<td>Probable</td>
<td>The AE is Likely Related to the intervention</td>
</tr>
<tr>
<td></td>
<td>Definite</td>
<td>The AE is Clearly Related to the intervention</td>
</tr>
</tbody>
</table>

**ATTRIBUTION**

For Each Event You Must Provide One Positive Attribution

- The adverse event, "Infections and infestations - Other: Treating for cellulitis," is not attributed to a cause. An attribution of possible or higher must be selected for at least one of the causes.
- Each Adverse Event needs one or more attributions of Possible, Probable, or Definite. An adverse event that resulted in death with AE term Death NOS, Sudden death NOS, Fetal death and Death neonatal is considered exempt from this requirement.
ATTRIBUTION

Information entered in any of the following areas will result in an attribution assignment being required

- Treatment agent(s)
- Cancer
- Concomitant Medication
- Contributing Cause

SAE REPORTING CRITERIA

- DEATH
- LIFE THREATENING EVENT
- INCAPACITATING EVENT
- REQUIRES/PROLONGS HOSPITALIZATION
- CONGENITAL ANOMALY
- OTHER MEDICALLY SIGNIFICANT EVENT
SECTION 16.1.f.

16.1 Adverse Event Reporting Requirements

f Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a CTEP IND:

1) Group-specific instructions.

Submission of the online CTEP-AERS report plus any necessary amendments generally complies with the reporting requirements. In addition, you may be asked to submit supporting clinical data to the SWOG Operations Office in order to complete the evaluation of the event. If requested, the supporting data should be sent within 5 calendar days by fax to 215-614-5000. Supporting clinical data submitted should include:

- Printed copy of the first page of the CTEP-AERS Report.
- Copies of clinical sourced documentation of the event.
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

2) The adverse events listed below also require expedited monitoring for this trial:

- Thrombotic events, any Grade regardless of attribution

3) For study arm(x)(applicable study arm(s)), the adverse events listed below do not require expedited reporting via CTEP-AERS:

- Grade 4 Hypersensitivity
- Grade 4 Infection
### Specific Protocol Exceptions to Expedited Reporting (SPEER)

<table>
<thead>
<tr>
<th>Adverse Events with Possible Relationship to Oxaliplatin (CTCAE 4.0 Term)</th>
<th>Specific Protocol Exceptions to Expedited Reporting (SPEER) (formerly known as ASAEL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Likely (&gt;20%)</td>
<td>Rare but Serious (&lt;3%)</td>
</tr>
<tr>
<td>Less Likely (&lt;=20%)</td>
<td></td>
</tr>
<tr>
<td>BLOOD AND LYMPHATIC SYSTEM DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>Anemia (Gr 4)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation</td>
<td>Disseminated Intravascular coagulation (Gr 4)</td>
</tr>
<tr>
<td>Fever/neutropenia</td>
<td>Fever/neutropenia (Gr 4)</td>
</tr>
<tr>
<td>Hemolysis</td>
<td>Hemolysis (Gr 1)</td>
</tr>
<tr>
<td>CARDIAC DISORDERS</td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Atrial fibrillation (Gr 4)</td>
</tr>
<tr>
<td>Atrial flutter</td>
<td>Atrial flutter (Gr 1)</td>
</tr>
<tr>
<td>Paroxysmal atrial tachycardia</td>
<td>Paroxysmal atrial tachycardia (Gr 2)</td>
</tr>
<tr>
<td>Sinus bradycardia</td>
<td>Sinus bradycardia (Gr 3)</td>
</tr>
<tr>
<td>Sinus tachycardia</td>
<td>Sinus tachycardia (Gr 2)</td>
</tr>
<tr>
<td>Supraventricular tachycardia</td>
<td>Supraventricular tachycardia (Gr 4)</td>
</tr>
<tr>
<td>Ventricular arrhythmia</td>
<td>Ventricular arrhythmia (Gr 4)</td>
</tr>
<tr>
<td>Ventricular fibrillation</td>
<td>Ventricular fibrillation (Gr 1)</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>Ventricular tachycardia (Gr 1)</td>
</tr>
</tbody>
</table>

### SAE Reporting Guidelines

**Commercial Agents**

<table>
<thead>
<tr>
<th>Attribution</th>
<th>Grade 4</th>
<th>Grade 5</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unexpected</td>
<td>Expected</td>
</tr>
<tr>
<td>Unrelated or Unlikely</td>
<td>AEERS</td>
<td>AEERS</td>
</tr>
<tr>
<td>Possible, Probable, Definite</td>
<td>AEERS</td>
<td>AEERS</td>
</tr>
</tbody>
</table>

**AEERS** indicates an expected report is to be submitted as a NOT AEERS within 10 calendar days of learning of the event.

- This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s), and is attributed (possible, probable, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

- Submission of the online AEERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be submitted within 10 calendar days by fax to 212-674-3006.
SAE REPORTING

ADVERSE EVENTS >30 DAYS AFTER INVESTIGATIONAL DRUG TREATMENT

May Meet Expedited Reporting Criteria

IF POSSIBLY, PROBABLY, OR DEFINITELY RELATED

[** Consult the Protocol **]

REPORTING A DEATH

Any death while on treatment or within 30 days of the last dose of study agent must be reported via CTEP-AERS
REPORTING A DEATH

- Death Attributable to CTCAE Term
- Death, NOS [If it cannot be attributed to a CTCAE term associated with Grade 5]
- Sudden Death NOS
- Death Due to Progressive Disease Should be Reported as Grade 5 ("Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)"")]
CTEP-AERS REPORT PATHWAYS

- 24-Hour Notification with a complete report due in 5 calendar days
- 10 Calendar Day report
- 24-Hour Amendment

24-HOUR NOTIFICATION
24-HOUR NOTIFICATION

Instructions: The table below summarizes reports for the given Ticket Number. Click Actions and select the option you wish to perform.

<table>
<thead>
<tr>
<th>Report Type</th>
<th>Amendment #</th>
<th>Report Submission Status</th>
<th>Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTEP Liquid/Report</td>
<td>0</td>
<td>Submitted successfully on 01/06/2016</td>
<td>Actions</td>
</tr>
<tr>
<td>CTEP 24 Hour Notification</td>
<td></td>
<td>Submitted successfully on 01/06/2016</td>
<td>Actions</td>
</tr>
</tbody>
</table>

An action is NOT recommended.

Possible exceptions (please consult your protocol for specific expedited reporting requirements):
- Commercial agent only studies
- Studies utilizing any of the legacy 40 Reporting tables (those that incorporate expediency and attribution into the table)
- Adverse events that occurred more than 30 days after the last administration of investigational agent
- Intervention or >10 radioactive half-lives for PET or SPECT agents.

Planned cases discussed: Theonucleoplasia, 2: >50,000 - 25,000/mL, <50.0 - 25.0 <50,000 - 25,000/mL, <25.0 - 25.0 x 10^5/mL

Available Actions

Based on the data you have entered and the rules enabled for this study, expedited reporting is not required. If you believe expedited reporting is warranted, click 'Override' and select the report you wish to complete.

Adverse Events

Override
PROVIDE "OUTCOME"

WHEN TO CREATE AN AMENDMENT

Follow the “One Ticket per Cycle” Rule
**DATE OF DISCOVERY**

Sites may not be aware of an event at the time it occurs – it is important to document date site is aware of an event if different from the dates of events reported on a CTEP-AERS report.
Pregnancy Reporting

Refer to Section 16.1 of the Protocol
Report via CTEP-AERS
NCI Pregnancy Reporting Form

- Pregnancy
- Fetal Death
- Death Neonatal

Recurrent SAEs

A recurrent is one that occurs and resolves during a cycle/course and then reoccurs in a later cycle or course

The SAE is reported at the first occurrence, and then reported again if reoccurs if it occurs and an increased grade or is associated with hospitalization
Persistent SAEs

A persistent SAE is one that extends continuously, without resolution between cycle/courses

The SAE must be reported only once unless the grade becomes more severe in the same or subsequent cycle/course

SECONDARY MALIGNANCY

A secondary malignancy is a cancer caused by treatment for a previous malignancy

A secondary malignancy is not considered a metastasis of the initial neoplasm
SECONDARY MALIGNANCY

Report under SOC “Neoplasms benign, malignant and unspecified (incl cysts and polyps) – CTCAE 4.0

- Leukemia secondary to oncology chemotherapy (e.g. AML)
- Myelodysplastic Syndrome (MDS)
- Treatment-related secondary malignancy

SECOND MALIGNANCY

A second malignancy (one unrelated to the treatment of a prior malignancy) or metastasis from the initial malignancy are not reported as an SAE

Routine Reporting Only
SUPPORTING DOCUMENTATION

SUPPORTING DOCUMENTATION TO BE SUBMITTED TO OPERATIONS OFFICE WITHIN 5 DAYS

• IF SWOG-HELD IND
• GRADE 5 EVENTS

This is a Separate submission from any documentation sent to NCI/CTEP
Submission Instructions - Section 16.1.f

SUPPORTING DOCUMENTATION

Remember to Protect Patient Privacy When Submitting Supporting Documentation

PT ID Number
Protocol Number
CTEP-AERS Ticket Number
Coversheet with Total Number of Pages
AUDITING

1) Consider the possibility that any AE could be reportable as an SAE. (Protocol Section 16)

2) If indicated, initiate a CTEP-AERS REPORT within 24 HOURS of the event or discovery of the event. (if unable to access the internet, contact the Operations office)

3) Submit the report within the PROTOCOL-SPECIFIC NUMBER OF CALENDAR DAYS

4) Send SUPPORTING DOCUMENTATION to the Operations office and NCI (as required / requested)

SWOG SAE REPORTING SUMMARY

Timely Reporting = Patient Safety & Regulatory Compliance
RESOURCES & SUPPORT

- General email:  [adr@swog.org](mailto:adr@swog.org) Attn: SAE Coordinator
- SWOG SAE Coordinator  phone: 210-614-8808 extension 1020  or email:  [kwilliams@swog.org](mailto:kwilliams@swog.org)
- SWOG Policy #23 available on SWOG website
- NCI Guidelines for Investigators:  Adverse Event Reporting Requirements (September 16, 2013)
RESOURCES & SUPPORT

For Information on CTEP-AERS application as well as training documents/slides can be found at:

http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

RESOURCES & SUPPORT

CTEP-AERS Medical Questions/Help:
Email: aemd@tech-res.com
Phone: (301) 897-7497
Fax: (301) 230-0159

CTEP-AERS Technical Questions/Help:
Email: ncictephelp@ctep.nci.nih.gov
Phone: 1-888-283-7457 or 301-840-8202