ADVERSE EVENT REPORTING MANUAL

Prepared by the

American College of Radiology Imaging Network

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1.0 Adverse Event Terminology and Definitions

1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a participant that does not necessarily have a causal relationship with the study intervention. An AE can therefore be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure.

1.2 Adverse Event Expedited Reporting System (AdEERS)

AdEERS is a web-based system created by the NCI for electronic submission of expedited AE reports.

1.3 Attribution

Attribution is a clinical determination, by the investigator, as to the likelihood that an AE is related to a medical treatment or procedure.

Attribution categories are:

Definite	The AE is ***clearly related*** to the treatment or procedure.
Probable	The AE is ***likely related*** to the treatment or procedure.
Possible	The AE ***may be related*** to the treatment or procedure.
Unlikely	The AE is ***doubtfully related*** to the treatment or procedure.
Unrelated	The AE is ***clearly NOT related*** to the treatment or procedure.

1.4 Baseline Adverse Event

A pre-existing condition or pertinent finding identified at baseline assessment.

1.5 C3D

C3D is an integrated clinical trial data collection and AE reporting system that allows for the reporting of ALL Adverse Events, including those also requiring expedited reporting via electronic AdEERS. Studies that will use C3D have been developed using C3D to create customized electronic case report forms (eCRFs).

1.6 Clinical Data Update System (CDUS)

CDUS is the data collection system used by the NCI Division of Cancer Treatment and Diagnosis (DCTD) to capture clinical data.

http://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/cdusv3.pdf

- CDUS-Abbreviated: Limited to protocol administrative and patient demographic information.

- CDUS-Complete: Includes all abbreviated CDUS information, plus treatment; adverse event, and response information.

1.7 Commercial Agent

Generally this refers to an agent that is marketed and is being used in a standard/labeled manner. A commercial agent may also be used as an

investigational agent (under an IND) when evaluating outside its approved, intended use.

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1.8 Common Terminology Criteria for Adverse Events (CTCAE)

The CTCAE contains descriptive terminology that is to be used for AE reporting. A grading (severity) scale is provided for each AE term.

1.9 Comprehensive Adverse Events & Potential Risks Lists (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AEs) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only.

1.10 Expected Adverse Event

An AE is considered expected when the event is listed in the protocol, and/or the Investigator's Brochure.

1.11 Expected – Indirect Adverse Event

An AE is determined to be expected-indirect when the event is associated with a procedure/medical treatment performed as a result of a positive finding on a screening imaging study and is listed either in the protocol or the Investigator's Brochure.

1.12 Expedited Reporting

Events that qualify for and require expedited reporting are defined per protocol and are submitted to and processed by the AdEERS system. Routine reporting requirements also apply.

While SAEs and unanticipated events frequently qualify for expedited reporting, the terms are not synonymous. All SAEs are NOT necessarily expedited reporting events. Expedited reporting events are not necessarily SAEs. The AE reporting section of the protocol governs reporting requirements.

1.13 Grade [Severity]

The Common Terminology Criteria for Adverse Events (CTCAE) is the key for assigning critical descriptors such as name and grade, to AEs. Grade is an essential element of AE Reporting and relates to the severity of an event or the purposes of regulatory reporting to NCI as follows:

1 Mild
2 Moderate
3 Severe
4 Life-threatening or disabling
5 Fatal

For terms listed in the CTCAE, the grade is still recorded as 1, 2, 3, 4 or 5; however, the definition of the various grades will be specific to the term being used.

NOTE: Severity is graded on a CTCAE based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness." Seriousness is a term that is used in guidance and regulatory documentation to determine reporting requirements.

1.14 Institutional Review Board (IRB)

A group convened and governed under FDA and other regulatory authority, consisting of scientists and non-scientists, and charged with the review and approval of research on human subjects. IRBs may also be referred to as Ethics Review Boards, as they are constituted to protect the rights and well being of people who take part in a clinical trial based upon ethical, scientific, and other principles. Typically, no human subject research specific activity may take place prior to IRB approval, and completion of the IRB defined Informed Consent process.

1.15 Investigational Agent

An investigational agent is any agent held under an Investigational New Drug (IND) application. It is a substance that has received FDA approval for use in human (clinical) research. An agent that has been approved by the FDA and labeled for use in a specific disease or condition at a specific dosing regimen would generally be considered investigational if it were being used in a clinical trial setting in a manner not reflective of its labeling. Also called experimental drug and investigational drug.

1.16 Life-Threatening Adverse Event

A life-threatening AE is any adverse event that places the participant, in the clinical opinion of the investigator, at immediate risk of death.

1.17 Routine Reporting

Documentation of study related AEs on the source documents and AE CRF, and submission to the sponsor for preparation of a report to various regulatory oversight committees and federal agencies.

1.18 Serious Adverse Event (SAE)

An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

1. Results in death or is life-threatening at the time of the event
2. Requires inpatient hospitalization, or prolongs a hospitalization
3. Results in a persistent or significant disability/incapacity
4. Is a congenital anomaly/birth defect (in a participants offspring)
5. Is medically judged to be an important event that jeopardized the subject and, for example, required significant measures to avoid one of the above outcomes.

1.19 Toxicity

Regulatory organizations have NOT clearly defined the term 'toxicity.' However, toxicity has been described as an AE that has an attribution of possibly, probably or definitely related to the investigational treatment. It is NCI's recommendation NOT to use the term toxicity for AE reporting purposes. The Common Toxicity Criteria for Adverse Events (CTCAE) was revised to the Common Terminology Criteria.

1.20 Unexpected Adverse Event

An unexpected AE is an event that is NOT listed in the protocol and/or the Investigator's Brochure.

1.21 Unexpected-Indirect Adverse Event

An unexpected-indirect AE is an event associated with a procedure/medical treatment performed as a result of a positive finding on a screening imaging study and NOT listed in the protocol and/or the Investigator's Brochure.

2.0 Adverse Event Reporting

Prompt reporting of AEs is the responsibility of each principal investigator and/or investigator designee (e.g. clinical research associate and/or nurse engaged in clinical research). Anyone uncertain about whether a particular AE should be reported should contact the American College of Radiology Imaging Network (ACRIN) Headquarters at (215)574-3150 and ask for the ACRIN AE Coordinator for further assistance.

Most ACRIN imaging studies will perform imaging with approved devices (or non-significant risk devices) and approved imaging agents with known favorable safety profiles. Under these circumstances, ACRIN protocols may limit the reporting of AEs to specific events, many of which would be expected to occur within 2 hours of the imaging procedure. However, study participants should be followed per protocol for the duration of their trial participation. The protocol will define the specific follow-up period (e.g. 30 days) and procedures, as well as reporting requirements.

2.1 Six (6) Categories of ACRIN Studies

- Diagnostic
- Screening
- Interventional
- Investigational Agents
- Investigational Devices
- Collaborative

2.2 Diagnostic

Typically these studies will use approved devices and imaging agents with known safety profiles. The protocol AE Reporting Section should follow imaging-only guidelines for reporting AEs.

2.3 Screening

Studies involving screening studies add a second dimension to monitoring and reporting of AEs. Two (2) additional categories of AEs, “expected-indirect” and “unexpected-indirect” AEs, should be considered. These are AEs that are associated with a procedure/medical treatment performed as a result of a positive finding on a screening imaging study.

2.4 Interventional

These interventional studies will be treated as therapeutic trials. The protocol AE reporting requirements will therefore follows all NCI/CTEP adverse event reporting guidelines.

2.5 Investigational Agents

The protocol for studies that use investigational agents [including agents used outside of their FDA approved labeling] must specify and meet all applicable regulations and guidance (e.g. NCI, FDA, ICH).

2.6 Investigational Devices

For studies that use investigational devices [including agents used outside of their FDA approved labeling], the protocol AE Reporting section must specify and meet all applicable regulations and guidance (e.g. NCI, FDA, ICH guidelines).

2.7 Collaborative

ACRIN continues to work in collaboration with other cooperative groups, complying with the NCI Cancer Therapy Evaluation Program (CTEP) rules of a lead group designation. For studies that involve a partnership with another cooperative group(s), the groups will define a mutually agreeable reporting process that is in compliance with all federal regulatory guidelines (e.g. NCI, FDA, ICH guidelines).

2.8 ACRIN Protocol Compliance

ACRIN protocols must comply with all applicable regulations and guidance. For the purposes of this manual, the NIH, NCI, OHRP, FDA, and other relevant federal/competent authorities' regulations and guidance dictates the reporting requirements for adverse events Complete and accurate reporting of AEs is the legal and ethical responsibility of the PI, assisted by investigator designees (e.g. clinical research associate and/or nurse engaged in clinical research) as appropriate. The accuracy and timeliness of reporting has implications both for the safety of research participants and for the validity of the data derived from clinical research.

2.9 Collection of Adverse Event Information

2.9.1 Site Responsibilities

Prompt reporting of adverse events is the responsibility of each investigator, clinical research associate and/or nurse engaged in clinical research. Adverse events should be followed by the investigator until the events are resolved, the subject is lost to follow-up, the condition is stabilized, or the adverse events are otherwise explained. Significant new information on any ongoing AEs/SAEs should be promptly reported to ACRIN and/or NCI/CIP.

2.9.2 Assignments of grades and attribution of each AE/SAE must be made by the site principal investigator. All AEs/SAEs are to be documented in the participant's study chart, AE case report form, and events that qualify for expedited reporting are to be submitted through the electronic AdEERS application**.**

2.9.3 At each contact (site visit and/or telephone) with the study participant, the investigator or qualified investigator-designee must elicit, through open ended questioning (e.g. "How are you feeling?") information on AEs, and if indicated, the participant should be evaluated clinically.

2.9.4 Steps to Initiate an Adverse Event Report

The following steps should be taken to initiate an AE report:

1. Identify the event.

2. Categorize the event within the parameters of the applicable version of CTCAE.
3. Grade the severity of the event within the parameters of the applicable version of CTCAE
4. Determine attribution of the AE per the protocol – assess the likelihood that the event is related to the study or imaging procedure using the protocol specified scale, ranging from Not Related to Definitely Related.
5. Determine if the AE is expected or unexpected based strictly upon the Investigators Brochure and/or Protocol AE/Risk section. When in doubt, consultation from ACRIN should be sought.
6. Determine how the event should be reported, given the relevant information above, and referencing the AE reporting section of the related protocol document.

2.10 Routine Adverse Event Reporting

For routine reporting, a completed ACRIN AE case report form must be submitted within 30 calendar days of first knowledge. However, it is important and strongly encouraged that the AE case report form is completed and submitted as soon as the relevant data are available. The protocol will define whether an adverse event will require routine reporting or both routine and expedited reporting.

2.11 Institutional Review Board (IRB) Reporting

Individual IRBs have policies that may differ with regard to AE and SAE reporting and reporting of Unanticipated Problems, which may include AEs or SAEs. Sites must be aware of the reporting requirements and timeframes imposed by their local IRB. Please refer to your local IRB of record for site specific reporting requirement.

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2.12 Questions regarding the AE Reporting Process

Timely reporting is crucial and questions regarding the reporting process should be directed to the ACRIN AE Coordinator. Contact the American College of Radiology at (215)574-3150 and ask for an ACRIN AE Coordinator.

3.0 Expedited Adverse Event Reporting

Adverse Event reporting is an essential component of a research study. Compliance with reporting ensures the safety and welfare of study participant, as well as data integrity. Certain events qualify for expedited reporting because, individually or in context, they may impact the continued use of an agent or the conduct of a trial. Prompt reporting of adverse events (AEs) is the responsibility of each site principal investigator (site PI). Anyone uncertain about whether a particular event should be reported should contact the American College of Radiology (ACR) Headquarters at (215)574-3150 and ask for the ACRIN AE Coordinator for further assistance.

National Cancer Institute – Cancer Imaging Program has provided adverse event reporting guidelines in the form of protocol templates. The templates can be found as attachments to the ACRIN Adverse Event Reporting Manual. The process for expedited AE reporting is outlined in these guidelines and the included tables contain clear and comprehensive instructions for AE evaluation and reporting. However, it should be noted that the protocol will define the specific reporting requirements.

All expedited adverse event reports (events submitted via AdEERS) are processed by an NCI contractor, currently Technical Resources International, Inc. (TRI). A TRI representative is available for assistance in the completion of the AdEERS report, and may be contacted as indicated below.

3.1 24 Hour Notification Process

Any AE/SAEs requiring 24 hour notification will either be reported electronically via the AdEERS application or through a telephone report. 24-hour notification provides an early detection mechanism for potential safety problems. Adverse events that must be reported within 24-hour of first knowledge are dependent upon the type of trial, the agent/intervention (investigational or commercial), whether expected or unexpected, grade, and attribution. To ensure vigilance for AE/SAEs that require 24-hour notification, AdEERS is programmed to facilitate timely submission.

3.1.1 24 Hour Electronic Reporting Instructions

All clinical studies conducted under an IND/IDE agent/device studies will submit 24-hour electronic notification within the AdEERS application. In the rare event when internet connectivity is disrupted a 24-hour notification is to be made by phone to CIP and ACRIN 24-hour telephone reporting lines.

NOTE: All clinical studies utilizing commercial agents must continue to use the 24-hour telephone notification reporting as described in Section 3.1.2.

3.1.2 24 Hour Telephone Reporting Instructions

Any AE/SAEs that require 24-hour notification as outlined in the study-specific protocol, please call the following numbers to report the event:

1. **CIP– SAE Reporting Line: (301)897-1704**

- The CIP-SAE reporting line is staffed Monday through Friday from 7:30am – 7:30pm ET (Eastern Time).
- AE/SAEs may be reported via voicemail during off hours.
- A TRI contact for AE/SAE reporting will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:

- Name of person reporting the AE/SAE and telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the adverse event
- Site principal investigator's assignment of the attribution of the adverse event (do not delay initial report if not available)

2. ACRIN–AE/SAE Reporting Line: (215)717-2763

- The ACRIN–AE/SAE reporting line is monitored by the ACRIN AE Coordinator: Monday through Friday from 8:30am – 4:30pm ET.
- AE/SAEs may be reported via voicemail during off hours.
- The ACRIN AE Coordinator will return your call within 24 hours.

Generally the following details are essential to initiate an AE/SAE report:

- Name of person reporting the AE/SAE, telephone number
- Institution name and institution number
- Protocol title and number
- Participant's case number and initials
- Site principal investigator's name and telephone number
- Date and time of the AE/SAE
- Date and time you learned of the AE/SAE
- Brief description of the AE/SAE
- Site principal investigator's assignment of the grade of the adverse event
- Site principal investigator's assignment of the attribution of the adverse event (do not delay initial report if not available)

IMPORTANT: After the 24 hour contact to CIP and ACRIN-AE/SAE reporting lines, an electronic Adverse Event Expedited Report (AdEERS) must be submitted per the protocol-specific requirements or the regulatory reporting timelines, if not specified in the protocol.

3.2 Adverse Event Expedited Reporting System (AdEERS)

Expedited adverse events are collected through the NCI Adverse Event Expedited Reporting System (AdEERS). AdEERS is a web-based system created by the NCI for the electronic submission of qualifying AE reports, as defined in each ACRIN protocol. It is broadly intended to capture and disseminate information on relatively significant adverse events, based upon trial stage, expectedness, grade, and attribution. All report sections identified as mandatory must be completed before CTEP will accept and process the report.

3.2.1 Submitting an AdEERS Report: Electronic Submission

Any AE/SAEs requiring expedited reporting must be submitted via the AdEERS web application. Please find the AdEERS application on the NCI/CTEP web page at: http://ctep.cancer.gov/reporting/adeers.html.

3.2.2 Submitting an AdEERS Report: System Unavailable

In the rare event that Electronic AdEERS [internet] access is unavailable; an AdEERS report may be submitted using the following process:

1. Download reporting forms in advance and store them locally for access in the event of internet unavailability.

   - http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers
   - The paper AdEERS forms can also be found on the ACRIN website. http://www.acrin.org/ADMINISTRATION/REGULATORYRESOURCES/tabid/495/Default.aspx

2. Choose Single or Multiple Agent template as appropriate.

   - Adverse Event Expedited Report – Single Agent Template: This template is used to report an AE for imaging studies and/or only one investigational agent.
   - Adverse Event Expedited Report – Multiple Agent Template: This template is used to report an AE for studies using more than one investigational agent. The template has additional space available to record up to four agents associated with the study.

3. Complete appropriate sections of the appropriate AdEERS form.

4. Fax the completed paper AdEERS report and any additional information (source documents) necessary for thorough review of the event(s) to (301)897-7402, attention CIP SAE Team.

5. Follow with an email to CIPSAEReporting@tech-res.com notifying the SAE Team that a paper AdEERS form and additional information (if available) has been faxed.

6. The submission process is NOT considered complete until an AdEERS report has been also submitted electronically by the original submitter at the site.

7. Once AdEERS access is restored, the paper AdEERS report must be entered electronically into the electronic AdEERS application by the original submitter at the site.

8. AdEERS is programmed for automatic electronic distribution of reports to the appropriate regulatory personnel including the study chair.

9. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure at (301)897-1704 and should be contacted to confirm receipt of materials sent during any period of AdEERS unavailability, or to provide guidance with the process as appropriate.

10. Routine reporting requirements also apply.

3.2.3 Assistance and Training Completing an AdEERS Report

For medical questions, contact AdEERSMD.
Phone: (301)897-7497
Email: adeersmd@tech-res.com.

For technical questions, contact the NCI Help Desk.
Phone: 1-888-283-7457
Email: ncictephelp@ctep.nci.nih.gov

Live Electronic AdEERS training can be coordinated for site personnel. Please contact the American College of Radiology at (215)574-3150 and ask for the ACRIN AE Coordinator to schedule electronic AdEERS training.

Electronic AdEERS training can be accessed on the web at http://www.acrin.org/ADMINISTRATION/REGULATORYRESOURCES/tabid/495/Default.aspx

3.3 ACRIN Contact for AE Reporting

The ACRIN AE Coordinator is available for any questions regarding the AE reporting process. Contact the American College of Radiology at (215)574-3150 and ask for an ACRIN AE Coordinator.

4.0 Reporting Requirements for Diagnostic Studies

Diagnostic imaging studies use approved imaging devices and/or imaging agents with known safety profiles within their approved labeling (commercial agents). Commercial agents are those agents not provided under the NCI IND, but obtained through a commercial source.

Certain protocols may call for a commercial agent to be used for an indication that is not included in the package label. On some occasions, NCI may distribute commercial supplies for a trial. In either case, the agent is still considered a commercial agent.

Due to the known safety profiles, adverse event reporting is anticipated to be minimal. General reporting requirements for such studies are outlined in the tables below, and provide guidance in developing protocol specific reporting requirements that supersede these recommendations.

4.1 Expedited Reporting Guidelines

For the complete NCI/CIP guidance document, refer to the appendix at the end of this document. However, it should be noted that the protocol will define the specific reporting requirements.

AdEERS Table for Reporting Commercial Agent Events:

TABLE A *[use for radioactive imaging agents]*

All Phases

AdEERS reporting requirements for adverse events occurring within 30 days the last study related procedure

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unex-pected	Expected	Unexpected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

TABLE A *[use for NON-radioactive imaging agents and studies that do not use imaging agents]*
All Phases
AdEERS reporting requirements for AEs occurring within 30 Days of the last study related procedure

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
		with Hospitalization	without Hospitalization		with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Expedited AE reporting timelines defined:

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

4.2 Routine Reporting Guidelines

All adverse events that require reporting per protocol **must** be reported in routine study data submissions. AEs reported through AdEERS must also be reported in routine study data submissions.

5.0 Reporting Requirements for Screening Studies

Screening imaging studies use approved imaging devices and/or imaging agents with known safety profiles within their approved labeling (commercial agents). Commercial agents are those agents not provided under the NCI IND, but obtained through a commercial source.

Certain protocols may call for a commercial agent to be used for an indication that is not included in the package label. On some occasions, NCI may distribute commercial supplies for a trial. In either case, the agent is still considered a commercial agent.

Due to the known safety profiles, adverse event reporting is anticipated to be minimal. General reporting requirements for such studies are outlined in the tables below, and provide guidance in developing protocol specific reporting requirements that supersede these recommendations.

5.1 Expedited Reporting Guidelines

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	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unex-pected	Expected	Unexpected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required
Possible Probable Definite	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

TABLE B *[use for NON-radioactive imaging agents and studies that do not use imaging agents]*
All Phases
AdEERS reporting requirements for AEs occurring within 30 Days of the last study related procedure

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unex-pected	Expected	Unexpected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Expedited AE reporting timelines defined:

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

5.2 Routine Adverse Event Reporting

All adverse events that require reporting per protocol **must** be reported in routine study data submissions. AEs reported through AdEERS must also be reported in routine study data submissions.

6.0 Reporting Requirements for Interventional Studies

Interventional studies using approved devices within labeled indications and with known safety profiles will follow the Commercial agent Adverse Event reporting table. Historically, the interventional trials have minimal adverse event reporting. However, the protocol specific reporting requirements will supersede these requirements. The reporting requirements will be developed on case by case basis per the study-related procedures and the safety profile of the approved device. The reporting requirements for interventional studies are outlined below.

6.1 Interventional Studies using Approved Medical Devices

Any AEs or SAEs identified to have occurred must comply with the reporting requirements as noted. Sites must comply with routine and/or expedited reporting requirements. Assignments of grades (severity level) and attribution for each AE is to be assessed at the site by the Site Principal Investigator.

Expedited reporting is required for the following:

- All unexpected Grade 4 (life-threatening) AEs within 30 days of the date of imaging/study related procedures attributed to the study intervention (possible, probable or definite) unless otherwise specified in the protocol;
- All (unexpected and expected) Grade 5 (fatal) AEs within 30 days of the date of imaging/study related procedures attributed to the study intervention (possible, probable or definite) unless otherwise specified in the protocol;
- Any death after 30 days of the last study procedure attributed to the study intervention (possible, probable or definite) should be reported within **10 calendar days** of first knowledge of the event.

NOTE: The protocol-specific AE guidelines would supersede the standard guidelines for AE reporting.

Reporting Requirements for Interventional Studies

The protocol-specific AE reporting requirements will be developed on case by case basis per the study-related procedures and the safety profile of the approved device. The protocol reporting requirements will supersede the guidelines below.

UNEXPECTED EVENT			EXPECTED EVENT		
Grades 1 – 3*† Attribution of Possible, Probable or Definite to the Study	**Grade 4†** Attribution of Possible, Probable or Definite to the Study	**Grade 5†** Attribution of Possible, Probable or Definite to the Study	**Grades 1 – 3*** Attribution of Possible, Probable or Definite to the Study	**Grade 4** Attribution of Possible, Probable or Definite to the Study	**Grade 5** Attribution of Possible, Probable or Definite to the Study
AE expedited reporting **NOT** required. Routine reporting requirements apply. ‡	AE expedited report required within **10 calendar days** of first knowledge of event. Routine reporting requirements also apply. ‡	Report by phone to **NCI** and **ACRIN** within **24 hours** of first knowledge of event. Expedited report completed and submitted within **10 calendar days** of first knowledge. Routine reporting requirements also apply. ‡	AE expedited reporting **NOT** required. Routine reporting requirements apply. ‡	AE expedited reporting **NOT** required. Routine reporting requirements apply. ‡	Report by phone to NCI and ACRIN within **24 hours** of first knowledge of the event. Expedited report completed and submitted within **10 calendar days** of first knowledge. Routine reporting requirements also apply. ‡

* Grade 1-3 AE expedited reporting is NOT required, unless it is otherwise specified in the protocol.
† All unexpected hospitalizations (or prolongation of existing hospitalization) for adverse events grade 3-5 and attribution of possible, probable or definite require an expedited report with in 10 calendar days of first knowledge, unless it is otherwise specified in the protocol.
‡ Submission of a completed ACRIN AE case report form within 30 calendar days of first knowledge.

NOTE: Adverse events that require 24-hour notification will be specified in the protocol. Refer to Sections 2.0 and 3.0 for details of adverse event reporting.

7.0 Reporting Requirements for Studies using Investigational Agents

Studies done under an investigational new drug (IND) application will need to comply with all federal regulatory guidelines, (e.g. NCI, FDA, ICH). Reporting will be handled in a protocol specific manner with templates driving protocol AE reporting section wording. Agents subject to radio-decay will be handled differently from those not subject to decay, and in addition reporting will differ according to trial phase, with phase 1 through early phase 2 trials being differentiated from late phase 2 through phase 3 trials.

7.1 Expedited Reporting Guidelines

For the complete NCI/CIP guidance document, refer to the appendix at the end of this document. However, it should be noted that the protocol will define the specific reporting requirements.

AdEERS Table for Reporting Phase 1 Through Early Phase 2 CIP IND Agent Events

TABLE A *[use for radioactive imaging agents]*

Phase 1 to Early Phase 2

AdEERS Reporting Requirements for Adverse Events occurring within [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] Day(s) +/- 4 hours of the last use of an agent held under CIP IND

	Grade 1	Grade 2		Grade 3				Grades 4 & 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for > 24 hours, due to adverse event.

NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

TABLE B *[use for NON-radioactive imaging agents]*
Phase 1 through early Phase 2
AdEERS Reporting Requirements for Adverse Events occurring within 30 Days of the last use of an agent held under CIP IND

	Grade 1	Grade 2		Grade 3				Grades 4 & 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for > 24 hours, due to adverse event.

NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

Expedited AE reporting timelines defined:

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

AdEERS Table for Reporting Late Phase 2 Through Phase 3 CIP IND Agent Events:

TABLE C *[use for radioactive imaging agents]*

Late Phase 2 Through Phase 3

AdEERS Reporting Requirements for Adverse Events occurring within [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] Day(s) +/- 4 hours of the last use of an agent held under CIP IND[1]

	Grade 1	Grade 2			Grade 3				Grades 4 & 5	
		Unexpected			Unexpected		Expected			
	Unexpected and Expected	with Hospital-ization	without Hospital-ization	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

NOTE: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

[1] Adverse events that occur more than [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] day(s) after the last dose of investigational agent and have an attribution of possible, probable, or definite require reporting as follows:

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

- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report-

- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

TABLE D *[use for NON-radioactive imaging agents]*
Late Phase 2 through Phase 3 Trials
AdEERS Reporting Requirements for Adverse Events occurring within 30 Days of the last use of an agent held under CIP IND[1]

	Grade 1	Grade 2			Grade 3				Grades 4 & 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization		
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

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

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

- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report-

- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following use of an agent under a CIP IND.

7.2 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine C3D/Complete CDUS study data submissions. AEs reported through AdEERS must also be reported in routine study data submissions.

8.0 Reporting Requirements for Studies using Investigational Devices

Studies using an investigational device must comply with all applicable federal and competent authority regulations and guidance, (e.g. NCI, FDA, ICH). Investigational device studies are governed by the FDA per the IDE, PMA, or 510(k) requirements.

When an investigational device(s) is used the device sponsor will define the reporting requirements which comply with the FDA device regulations and will supersede the standard NCI guidelines for adverse event reporting. Device sponsors comply with the Code of Federal Regulation (21 CFR §803) in defining the reporting requirements for the investigational device(s). Investigational medical device reporting process and timelines are distinctive that the non-investigational and interventional trials. Refer to the protocol for specific reporting requirements. FDA link to the device reporting requirements is available in the Chapter 10.

9.0 Reporting Requirements for Collaborative Clinical Studies

ACRIN is cognizant that imaging plays a significant role in cancer care. ACRIN has taken numerous steps to engage the broader oncology research community. This is accomplished through extensive collaboration with other cooperative groups. ACRIN continues to work in collaboration with other cooperative groups, complying with the NCI Cancer Therapy Evaluation Program (CTEP) rules of a lead group designation.

In collaborative trials, ACRIN will oversee the imaging component of the trial, including expedited reporting requirements of any investigational contrast agent. Reporting requirements will comply with IND trials (Chapter 7).

The other cooperative group will oversee the treatment and/or surgical component, including reporting cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols.

For collaborative clinical studies, groups will define the adverse event reporting process. The protocol will contain clear, specific, and complete reporting requirements for each component of the study. Collection and reporting of adverse events is the responsibility of each site principal investigator.

10.0 Additional Resources

- **ACRIN Protocol Development and Regulatory Resources:**

  http://www.acrin.org/ADMINISTRATION/REGULATORYRESOURCES/tabid/495/Default.aspx

- **AdEERS Computer Based Training:**

  http://ctep.cancer.gov/reporting/AdEERS_CBT_v3/welcome.html

- **AdEERS Multiple Agent Report:**

  http://ctep.cancer.gov/forms/34-AdEERS_v3-0_MAT_11-21-00.pdf

- **AdEERS Resources:**

  http://ctep.info.nih.gov/reporting/adeers.html

- **AdEERS Single Agent Report:**

  http://ctep.cancer.gov/forms/34-AdEERSv4_SAT.pdf

- **National Cancer Institute (NCI):**

  http://www.cancer.gov/

- **NCI Reporting Guidelines:**

  http://ctep.info.nih.gov/reporting/index.html

- **NCI Cancer Imaging Program:**

  http://imaging.cancer.gov/

- **NCI Cancer Therapy Evaluation Program – Adverse Events/AdEERS:**

  http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

- **U.S. Food and Drug Administration (FDA):**

  http://www.fda.gov/

- **FDA Medical Devices/Device Regulations and Guidance**

  http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/default.htm

11.0 Appendix

National Cancer Institute – Cancer Imaging Program have provide an adverse event reporting guidelines for the ACRIN Adverse Event Reporting Manual. The process for expedited AE reporting is outlined in these guidelines and the included tables contain clear and comprehensive instructions for AE evaluation and reporting.

It should be noted that the protocol will define the specific reporting requirements.

Appendix 1 – Protocol Template for Risk and Adverse Event Sections for Phase 1 through Early Phase 2 CIP-IND Imaging Agent Trials (11 pages)

Appendix 2 – Protocol Template for Risk and Adverse Event Sections for Late Phase 2 through Phase 3 CIP-IND Imaging Agent Trials (10 pages)

Appendix 3 – Protocol Template for Risk and Adverse Event Sections for Commercial Non-IND Imaging Agent Trials (10 pages)

National Cancer Institute

Cancer Imaging Program

"Generic" Protocol Template for Risk and Adverse Event Sections

CIP-IND Imaging Agent Trials

Phase One through Early Phase Two

[Adapted from NCI-CTEP Risk & AE Reporting Guidance & Template]

VERSION: 3.0.0

EFFECTIVE: September 10, 2009

The template contains imbedded instructions and commentary.

Template Text Conventions & Comments:

- ***Explanatory text*** *NOT FOR USE IN PROTOCOL is generally in italics or highlighted italics.*.
- Template text appears as normal or **normal/bold** text.
- Study specific areas to be filled in appear in [brackets with yellow highlight].

CIP Phase 1 through early Phase 2 Imaging Agent AE template begins on next line:

[AE Section Numeral] STUDY SPECIFIC RISKS/ADVERSE EVENT REPORTING

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the Adverse Event Expedited Reporting System (AdEERS) application. All Adverse Events, as defined herein, will, in addition, be reported via CDUS Complete, C3D, or other AE reporting system as specified below.

AdEERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if AdEERS reporting is required per protocol.

For this study, Adverse Event reporting must follow the guidelines and timing requirements below. The latest version of the NCI/CTEP Adverse Event Reporting Requirements document, which is available at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

provides additional details, and may be consulted as a reference, but **does not supersede AE reporting as specified in this protocol.**

The electronic-AdEERS AE system is to be used for all 'expedited reporting' events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. Expedited AE data is to be re-submitted via the

electronic AdEERS system as soon as is possible in cases where temporary e-AdEERS unavailability has necessitated manual capture and submission.

[Subsection Numeral]General Definitions

Adverse Event (AE): For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant **during the Adverse Event reporting period defined in table '[A]' of the protocol**, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, **regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.**

If there is thought to be a conflict between the protocol and a regulatory or guidance source, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participants offspring)

Adverse Event Expedited Reporting System (AdEERS): AdEERS is a web-based system created by NCI for electronic submission of expedited AE reports & is to be used in this study.

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study, [____name of agent___] is an investigational agent.

Commercial Agent: A commercial agent is any agent marketed and obtained from a commercial source. In this study [____name of agent(s)_____] is/are (a) commercial agent(s).

Clinical Data Update System (CDUS/Complete CDUS): CDUS/CompleteCDUS is a data collection system used to capture clinical data. Complete CDUS is capable of capturing Adverse Event Data and [is/is **NOT**] being used in this study. [See C3D, below.]

C3D: C3D is an integrated clinical trial data collection and AE reporting system for

reporting of ALL Adverse Events, including those also requiring expedited reporting via (e)-AdEERS. Trials that will use C3D have been developed using C3D to create customized eCRFs.

This trial [will/will not] use C3D. [See CDUS above.]

[subsection numeral] AE Reporting Requirements

The list of AEs [see CAEPR/ASAEL below, section [CAEPR/ASAEL subsection number]], and the characteristics of an observed AE [see "Adverse Event Characteristics - Definitions" below, section ["AE Characteristics-Definitions" subsection number]] will determine whether the event requires expedited (via electronic-AdEERS) reporting **in addition** to routine (via [C3D/Complete CDUS]) reporting.

NOTE: 24-Hour Notification for CIP IND Trials

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade, and attribution. Table "[A]" and footnotes to the table outline 24-hour notification requirements for AEs in trials utilizing an agent under a CIP IND. Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS. To ensure vigilance for AEs that require 24-hour notification, AdEERS is programmed to facilitate complete, timely submission.

[subsection numeral] Comprehensive Adverse Events & Potential Risks Lists (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AEs) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. **This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only.**

CAEPR & ASAEL have been consulted in compiling the Adverse Events list in this protocol and the Informed Consent for the study.

Please refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.

pdf

for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information.

[subsection numeral] CAEPR for [CIP IND Agent #1]

[Insert the CAEPR for agent #1 here.]

[subsection numeral] CAEPR for [CIP IND Agent #2]

[Insert the CAEPR for agent #2 here.]

[subsection numeral] Adverse Event List(s) for [Other Investigational Agent(s) *{use or delete this section as necessary and repeat for each agent as necessary}*]

[Insert the AE list here]

*[**NOTE**: This section is for an investigational agent not supplied by CIP, such as a treatment drug for which CTEP holds the IND. Include a comprehensive list of all reported adverse events and any potential risks such as:*

- *Adverse events associated with another agent of the same class*
- *Adverse event risks based upon pre-clinical evaluation*
- *Adverse event risks based upon the mechanism of action*
- *Adverse event risks based upon the chemical class or vehicle*
- *Adverse event risks based upon how the agent is administered*

Be sure to include risks included in the IB or those reported in other trials of the agent, or other documentation.]

[subsection numeral] Adverse Event List(s) for [Commercial Agent(s)]

[Insert the AE list here]

[NOTE**: This section is for a marketed agent. Based upon the package insert, the **most common and the most serious risks must, as a minimum**, be included, so that **any events not included are BOTH uncommon AND not serious.]

[subsection numeral] Adverse Event Characteristics

Expected Adverse Event: An expected AE is an event that is listed in the protocol or the Investigator's Brochure.

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the protocol or the Investigator's Brochure.

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure

Grade: Grade denotes the **severity** of the AE. An AE is graded using the following categories:

- **Mild**
- **Moderate**
- **Severe**
- **Life-threatening or disabling**
- **Fatal**

NOTE: Severity is graded on a CTCAE based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness," which is an overall assessment [See SAE above] that determines reporting requirements.

[subsection numeral] CTCAE term (AE description and grade)

The descriptions and grading scales found in the most recent release version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the most current CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).]

[subsection numeral] Expectedness

AEs can be 'Unexpected' or 'Expected' [see above] for expedited reporting purposes only. 'Expected' AEs (i.e., the ASAEL) are bold and italicized in the CAEPR.

[subsection numeral] Expedited Adverse Event Reporting

Expedited AE reporting for this study must use electronic AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in Table "[A]" below.

In the rare event that Electronic AdEERS [internet] access is lost, an AE report may be submitted using the following process:

1. Sites should download reporting forms in advance and store them locally for access in the event of internet unavailability. They can be found at:

   http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

2. Site chooses Single or Multiple Agent template as appropriate

3. Site completes appropriate sections of the SAE submission form.

   NOTE: For 24-hour notification, site follows up with a faxed SAE submission within 5 business days.

4. Site faxes SAE submission form and any additional information (source documents) necessary for thorough review of the event(s) along with the SAE submission form to 301-897-7402, attention CIP SAE Team. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure (Tel. 301-897-7497), and should be contacted to confirm receipt of materials sent during any period of AdEERS unavailability, or to provide guidance with the process as appropriate.

5. Site follows up with an email to CIPSAEReporting@tech-res.com notifying the SAE Team that an SAE form and additional information (if available) has been faxed.

6. **For IND studies:** the submission process is not considered complete until an AdEERS report has been submitted electronically.

7. Once AdEERS access is restored, an AE report submitted by the backup process must be entered electronically into AdEERS by the original submitter at the site.

8. AdEERS will be programmed for automatic electronic distribution of reports to the following individuals:

[insert list of CIP, Protocol, Cooperative Group & Other AE Notifications.
AdEERS provides a copy feature for other e-mail recipients]

[subsection numeral] Expedited Reporting Guidelines

*[**Select ONE** of the tables below (both are labeled 'A') and include WITH explanatory notes at the bottom of the box. **The first table** is to be used for agents that undergo **radioactive decay** such as labeled PET or SPECT agents. The **second table** should be selected for studies of **non-radioactive** imaging agents (e.g. MRI or US agents)]:*

ADEERS TABLE for REPORTING PHASE 1 THROUGH EARLY PHASE 2 CIP IND

AGENT EVENTS:

TABLE A *[use for radioactive imaging agents]*
Phase 1 to Early Phase 2
AdEERS Reporting Requirements for Adverse Events occurring within [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] Day(s) +/- 4 hours of the last use of an agent held under CIP IND

	Grade 1	Grade 2		Grade 3				Grades 4 & 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

TABLE A *[use for NON-radioactive imaging agents]*
Phase 1 through early Phase 2
AdEERS Reporting Requirements for Adverse Events occurring within 30 Days of the last use of an agent held under CIP IND

	Grade 1	Grade 2		Grade 3				Grades 4 & 5
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected and Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

[subsection numeral] Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following use of an agent under a CIP IND.

[subsection numeral] Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, eAdEERS). The following AEs must still be reported through the routine C3D/Complete CDUS reporting mechanism:

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

[subsection numeral] Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine C3D/Complete CDUS study data submissions. **AEs reported through AdEERS must <u>also</u> be reported in routine study data submissions.**

[subsection numeral] <u>Secondary AML/MDS</u>

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the <u>NCI/CTEP Secondary AML/MDS Report Form.</u> This form can be downloaded from the CTEP web site (http://ctep.cancer.gov). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

National Cancer Institute

Cancer Imaging Program

"Generic" Protocol Template for Risk and Adverse Event Sections

CIP-IND Imaging Agent Trials

Late Phase 2 through Phase 3

[Adapted from NCI-CTEP Risk & AE Reporting Guidance & Template]

VERSION: 3.0.0

EFFECTIVE: September 10, 2009

The template contains imbedded instructions and commentary.

Template Text Conventions & Comments:

- ***Explanatory text*** *NOT FOR USE IN PROTOCOL is generally in italics or highlighted italics.*.
- Template text appears as normal or **normal/bold** text.
- Study specific areas to be filled in appear in [brackets with yellow highlight].

CIP late Phase 2 through Phase 3 Imaging Agent AE template begins on next line:

[AE Section Numeral] STUDY SPECIFIC RISKS/ADVERSE EVENT REPORTING

Qualifying Adverse Events (AEs), including Serious Adverse Events (SAEs), as defined herein, will be reported via the Adverse Event Expedited Reporting System (AdEERS) application. All Adverse Events, as defined herein, will, in addition, be reported via CDUS Complete, C3D, or other AE reporting system as specified below.

AdEERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if AdEERS reporting is required per protocol.

For this study, Adverse Event reporting must follow the guidelines and timing requirements below. The latest version of the NCI/CTEP Adverse Event Reporting Requirements document, which is available at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

provides additional details, and may be consulted as a reference, but **does not supersede AE reporting as specified in this protocol.**

The electronic-AdEERS AE system is to be used for all 'expedited reporting' events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. Expedited AE data is to be re-submitted via the electronic AdEERS system as soon as is possible in cases where temporary e-AdEERS unavailability has necessitated manual capture and submission.

[Subsection Numeral]General Definitions

Adverse Event (AE): For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant **during the Adverse Event reporting period defined in table '[A]' of the protocol**, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, **regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.**

If there is thought to be a conflict between the protocol and a regulatory or guidance source, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization
- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participants offspring)

Adverse Event Expedited Reporting System (AdEERS): AdEERS is a web-based system created by NCI for electronic submission of expedited AE reports & is to be used in this study.

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. For purposes of this study, [____name of agent___] is an investigational agent.

Commercial Agent: A commercial agent is any agent marketed and obtained from a commercial source. In this study [____name of agent(s)_____] is/are (a) commercial agent(s).

Clinical Data Update System (CDUS/Complete CDUS): CDUS/CompleteCDUS is a data collection system used to capture clinical data. Complete CDUS is capable of capturing

Adverse Event Data and [is/is **NOT**] being used in this study. [See C3D, below.]

C3D: C3D is an integrated clinical trial data collection and AE reporting system for reporting of ALL Adverse Events, including those also requiring expedited reporting via (e)-AdEERS. Trials that will use C3D have been developed using C3D to create customized eCRFs.

This trial [will/will not] use C3D. [See CDUS above.]

[subsection numeral] AE Reporting Requirements

The list of AEs [see CAEPR/ASAEL below, section [CAEPR/ASAEL subsection number]], and the characteristics of an observed AE [see "Adverse Event Characteristics - Definitions" below, section ["AE Characteristics-Definitions" subsection number]] will determine whether the event requires expedited (via electronic-AdEERS) reporting **in addition** to routine (via [C3D/Complete CDUS]) reporting.

NOTE: 24-Hour Notification for CIP IND Trials

The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade, and attribution. Table "[A]" and footnotes to the table outline 24-hour notification requirements for AEs in trials utilizing an agent under a CIP IND. Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS. To ensure vigilance for AEs that require 24-hour notification, AdEERS is programmed to facilitate complete, timely submission.

[subsection numeral] Comprehensive Adverse Events & Potential Risks Lists (CAEPR)

The Comprehensive Adverse Event and Potential Risks list (CAEPR) provides a single, complete list of reported and/or potential adverse events (AEs) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Agent Specific Adverse Event List (ASAEL), appears in a separate column and is identified with bold and italicized text. **This subset of AEs (the ASAEL) contains events that are considered 'expected' for expedited reporting purposes only.**

CAEPR & ASAEL have been consulted in compiling the Adverse Events list in this protocol and the Informed Consent for the study.

Please refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

for further clarification. The CAEPR does not provide frequency data; refer to the Investigator's Brochure for this information.

[subsection numeral] CAEPR for [CIP IND Agent #1]

[Insert the CAEPR for agent #1 here.]

[subsection numeral] CAEPR for [CIP IND Agent #2]

[Insert the CAEPR for agent #2 here.]

[subsection numeral] Adverse Event List(s) for [Other Investigational Agent(s) *{use or delete this section as necessary and repeat for each agent as necessary}*]

[Insert the AE list here]

*[**NOTE**: This section is for an investigational agent not supplied by CIP, such as a treatment drug for which CTEP holds the IND. Include a comprehensive list of all reported adverse events and any potential risks such as:*

- *Adverse events associated with another agent of the same class*
- *Adverse event risks based upon pre-clinical evaluation*
- *Adverse event risks based upon the mechanism of action*
- *Adverse event risks based upon the chemical class or vehicle*
- *Adverse event risks based upon how the agent is administered*

Be sure to include risks included in the IB or those reported in other trials of the agent, or other documentation.]

[subsection numeral] Adverse Event List(s) for [Commercial Agent(s)]

[Insert the AE list here]

[NOTE**: This section is for a marketed agent. Based upon the package insert, the **most common and the most serious risks must, as a minimum**, be included, so that **any events not included are BOTH uncommon AND not serious.]

[subsection numeral] Adverse Event Characteristics

Expected Adverse Event: An expected AE is an event that is listed in the protocol or the Investigator's Brochure.

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the protocol or the Investigator's Brochure.

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure

Grade: Grade denotes the **severity** of the AE. An AE is graded using the following categories:

- **Mild**
- **Moderate**
- **Severe**
- **Life-threatening or disabling**
- **Fatal**

NOTE: Severity is graded on a CTCAE based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness," which is an overall assessment [See SAE above] that determines reporting requirements.

[subsection numeral] CTCAE term (AE description and grade)

The descriptions and grading scales found in the most recent release version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the most current CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).]

[subsection numeral] Expectedness

AEs can be 'Unexpected' or 'Expected' [see above] for expedited reporting purposes only. 'Expected' AEs (i.e., the ASAEL) are bold and italicized in the CAEPR.

[subsection numeral] Expedited Adverse Event Reporting

Expedited AE reporting for this study must use electronic AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in Table "[A]" below.

In the rare event that Electronic AdEERS [internet] access is lost, an AE report may be submitted using the following process:

1. Sites should download reporting forms in advance and store them locally for access in the event of internet unavailability. They can be found at:

   http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

2. Site chooses Single or Multiple Agent template as appropriate.

3. Site completes appropriate sections of the SAE submission form.

   NOTE: For 24-hour notification, site follows up with a faxed SAE submission within 5 business days.

4. Site faxes SAE submission form and any additional information (source documents) necessary for thorough review of the event(s) along with the SAE submission form to 301-897-7402, attention CIP SAE Team. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure (Tel. 301-897-7497), and should be contacted to confirm receipt of materials sent during any period of AdEERS unavailability, or to provide guidance with the process as appropriate.

5. Site follows up with an email to CIPSAEReporting@tech-res.com notifying the SAE Team that an SAE form and additional information (if available) has been faxed.

6. **For IND studies:** the submission process is not considered complete until an AdEERS report has been submitted electronically.

7. Once AdEERS access is restored, an AE report submitted by the backup process must be entered electronically into AdEERS by the original submitter at the site.

8. AdEERS will be programmed for automatic electronic distribution of reports to the following individuals:

[insert list of CIP, Protocol, Cooperative Group & Other AE Notifications.
AdEERS provides a copy feature for other e-mail recipients]

[subsection numeral] Expedited Reporting Guidelines

*[**Select ONE** of the tables below(both are labeled 'A') and include WITH explanatory notes. **The first table** is to be used for agents that undergo **radioactive decay** such as labeled PET or SPECT agents. The **second table** should be selected for studies of **non-radioactive** imaging agents (e.g. MRI or US agents)]:*

ADEERS TABLE for REPORTING LATE PHASE 2 THROUGH PHASE 3 CIP IND

AGENT EVENTS:

TABLE A *[use for radioactive imaging agents]*
Late Phase 2 Through Phase 3
AdEERS Reporting Requirements for Adverse Events occurring within [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] Day(s) +/- 4 hours of the last use of an agent held under CIP IND

	Grade 1	Grade 2			Grade 3				Grades 4 & 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization		
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

1 **Adverse events that occur more than [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] day(s) after the last dose of investigational agent and have an attribution of possible, probable, or definite require reporting as follows:**

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

- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report-

- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

TABLE A *[use for NON-radioactive imaging agents]*

Late Phase 2 through Phase 3 Trials

AdEERS Reporting Requirements for Adverse Events occurring within 30 Days of the last use of an agent held under CIP IND

	Grade 1	Grade 2			Grade 3				Grades 4 & 5	
		Unexpected			Unexpected		Expected			
	Unexpected and Expected	with Hospital-ization	without Hospital-ization	Expected	with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	Not Required	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

2 **Adverse events that occur more than 30 days after the last dose of investigational agent and have an attribution of possible, probable, or definite require reporting as follows:**

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

- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report-

- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

[subsection numeral] Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following use of an agent under a CIP IND.

[subsection numeral] Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, eAdEERS). The following AEs must still be reported through the routine C3D/Complete CDUS reporting mechanism:

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

[subsection numeral] Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine C3D/Complete CDUS study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.**

[subsection numeral] Secondary AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP web site (http://ctep.cancer.gov). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.

National Cancer Institute

Cancer Imaging Program

"Generic" Protocol Template for Risk and Adverse Event Sections

Commercial [Non-IND] Imaging Agent Trials

All Phases

[Adapted from NCI-CTEP Risk & AE Reporting Guidance & Template]

VERSION: 3.0.1

EFFECTIVE: September 29, 2009

The template contains imbedded instructions and commentary.

Template Text Conventions & Comments:

- ***Explanatory text*** *NOT FOR USE IN PROTOCOL is generally in italics or highlighted italics.*.
- Template text appears as normal or **normal/bold** text.
- Study specific areas to be filled in appear in [brackets with yellow highlight].

CIP Commercial Imaging Agent AE template begins on next line:

[AE Section Numeral] STUDY SPECIFIC RISKS/ADVERSE EVENT REPORTING

Adverse events(AEs) meeting the criteria in the tables below, including all serious adverse events (SAEs) will be reported to the Cancer Imaging Program (CIP) as directed in this section.

AdEERS is an electronic, internet based expedited Adverse Event reporting system operated by NCI/CTEP. It is generally used to capture and disseminate information on relatively significant Adverse Events, based upon trial stage, expectedness, severity, and attribution. However, it may be used to report adverse events of all types if AdEERS reporting is required per protocol.

For this study, Adverse Event reporting must follow the guidelines and timing requirements below. The latest version of the NCI/CTEP Adverse Event Reporting Requirements document, which is available at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

provides additional details, and may be consulted as a reference, but **does not supersede AE reporting as specified in this protocol.**

The electronic-AdEERS AE system is to be used for all 'expedited reporting' events as defined herein. If the system is temporarily unavailable, a paper and telephone/FAX based process is provided herein. Expedited AE data is to be re-submitted via the electronic AdEERS system as soon as is possible in cases where temporary e-AdEERS unavailability has necessitated manual capture and submission.

[Subsection Numeral]General Definitions

Adverse Event (AE): For the purpose of this study, an Adverse Event is an untoward medical condition experienced by a study participant **during the Adverse Event reporting period defined in [table '[A]' or elsewhere in] the protocol**, or by applicable guidance, regulation, or policy. An AE is any unfavorable or unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with participation in the study, **regardless of exposure to an agent or procedure, and regardless of whether it is considered to be caused by the agent, device, or process under investigation.**

If there is thought to be a conflict between the protocol and a regulatory or guidance source, consult the CIP Clinical Trials Branch. If a decision must be made pending final clarification, the stricter requirement should be applied.

Life-Threatening Adverse Event: A life-threatening AE is any adverse event that places the study participant, in the clinical opinion of the investigator, at immediate risk of death.

Serious Adverse Event (SAE): An SAE is defined as any untoward medical occurrence that meets any one of the following criteria:

- Results in death or is life-threatening at the time of the event
- Requires inpatient hospitalization, or prolongs a hospitalization

  NOTE: Hospitalization for expedited AE reporting purposes is a medically required inpatient hospital stay equal to or greater than 24 hours. Hospitalization is used as an indicator of the seriousness of the adverse event and should be reserved for situations where the adverse event truly fits this definition, and not for hospitalizations associated with less serious events. For example, a hospital visit where a subject is admitted for observation or minor treatment (e.g., hydration), and released in less than 24 hours, generally is not intended, in and of itself, to qualify as an SAE. Furthermore, hospitalization for pharmacokinetic sampling, is not an AE, and therefore is not to be reported either as a routine AE or in an expedited report. Hospitalization or prolongation of hospitalization associated with Grade 3 events, unexpected and expected, and regardless of attribution; require expedited reporting for trials utilizing an agent under a CTEP IND. As in all cases, if there is any doubt as to reporting an event, the CIP SAE reporting desk help line is to be consulted promptly.

- Results in a persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in a participants offspring)

All SAEs are to be followed by the investigator until resolution, stabilization, scientifically and clinically satisfactory explanation as to attribution and etiology, or until subject is lost to follow up.

Adverse Event Expedited Reporting System (AdEERS): AdEERS is a web-based system created by NCI for electronic submission of SERIOUS and/or UNEXPECTED AE reports &

is to be used in this study. All CIP trials must use AdEERS for expedited reporting of AEs resulting from:

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

Investigational Agent: An investigational agent is any agent held under an Investigational New Drug (IND) application. In this study, there are no investigational agents.

Commercial Agent: A commercial agent is any agent marketed and obtained from a commercial source, and used under approved label indication. In this study [name of agent(s)] is/are (a) commercial agent(s).

[subsection numeral] AE Reporting Requirements

The list of AEs, and the characteristics of an observed AE [see "Adverse Event Characteristics - Definitions" below, section ["AE Characteristics-Definitions" subsection number]] will determine whether the event requires expedited (via electronic-AdEERS) reporting **in addition** to routine reporting. For this study AdEERS reporting will be done electronically.

NOTE: 24-Hour Notification for CIP-IND or Non-IND Trials
The adverse event 24-hour notification requirement provides an early detection system for potential safety problems. Adverse events that must be reported within 24-hours of learning of the event are dependent upon the phase of trial, the agent/intervention (investigational or commercial), whether the event is expected or unexpected, the grade and attribution. Table "[A]" outlines 24-hour notification requirements for AEs. Adverse events that fulfill the 24-hour reporting requirement must be reported electronically via AdEERS. To ensure vigilance for AEs that require 24-hour notification, AdEERS is programmed to facilitate complete, timely submission.

[subsection numeral] Adverse Events & Risks

Please refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" at

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/newadverse_2006.pdf

and refer to the Investigator's Brochure for this information.

[subsection numeral] Adverse Event List(s) for [Commercial Agent(s)]

[Insert the AE list here]

[NOTE**: This section is for a marketed agent. Based upon the package insert, the **most common and the most serious risks must, as a minimum**, be included, so that **any events not included are BOTH uncommon AND not serious.]

[subsection numeral] Adverse Event Characteristics

Expected Adverse Event: An expected AE is an event that is listed in the protocol or the Investigator's Brochure.

Unexpected Adverse Event: An unexpected AE is an event that is NOT listed in the protocol or the Investigator's Brochure.

Attribution: Attribution is a clinical determination, by the investigator, as to whether an AE is related to a medical treatment or procedure. Attribution categories are:

- **Definite:** The AE is **clearly related** to a treatment or procedure
- **Probable:** The AE is **likely related** to a treatment or procedure
- **Possible:** The AE **may be related** to a treatment or procedure
- **Unlikely:** The AE is **likely unrelated** to a treatment or procedure
- **Unrelated:** The AE is **clearly not related** to a treatment or procedure

Grade: Grade denotes the **severity** of the AE. An AE is graded using the following categories:

- **Mild**
- **Moderate**
- **Severe**
- **Life-threatening or disabling**
- **Fatal**

NOTE: Severity is graded on a CTCAE based scale for each CTCAE event. For example, an abnormal hemoglobin value is graded for severity from 1 to 5 [death] based upon where that value falls on the CTCAE scale of abnormal Hemoglobin values. "Severity" is NOT the same as "Seriousness," which is an overall assessment [See SAE above] that determines reporting requirements.

[subsection numeral] CTCAE term (AE description and grade)

The descriptions and grading scales found in the most recent release version of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. All appropriate clinical areas should have access to a copy of the most current CTCAE. A copy of the CTCAE can be downloaded from the CTEP web site (http://ctep.cancer.gov).]

[subsection numeral] Expectedness

AEs can be 'Unexpected' or 'Expected' [see above] for expedited reporting purposes only. 'Expected' AEs are taken from the Package Insert.

[subsection numeral] Expedited Adverse Event Reporting

Expedited AE reporting for this study must use electronic AdEERS (Adverse Event Expedited Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). Site personnel will be trained in required AE identification and reporting procedures. These requirements are briefly outlined in Table "[A]" below.

In the rare event that Electronic AdEERS [internet] access is lost, an AE report may be submitted using the following process:

1. Sites should download reporting forms in advance and store them locally for access in the event of internet unavailability. They can be found at:

   http://ctep.cancer.gov/protocolDevelopment/default.htm#adverse_events_adeers

2. Site chooses Single or Multiple Agent template as appropriate

3. Site completes appropriate sections of the SAE submission form.

   NOTE: For 24-hour notification, site follows up with a faxed SAE submission within 5 business days.

4. Site faxes SAE submission form and any additional information (source documents) necessary for thorough review of the event(s) along with the SAE submission form to 301-897-7402, attention CIP SAE Team. The CIP SAE Reporting Desk may be contacted for assistance with any part of this procedure (Tel. 301-897-7497), and should be contacted to confirm receipt of materials sent during any period of AdEERS unavailability, or to provide guidance with the process as appropriate.

5. Site follows up with an email to CIPSAEReporting@tech-res.com notifying the SAE Team that an SAE form and additional information (if available) has been faxed.

6. **For IND studies:** the submission process is not considered complete until an AdEERS report has been submitted electronically.

7. Once AdEERS access is restored, an AE report submitted by the backup process must be entered electronically into AdEERS by the original submitter at the site.

8. AdEERS will be programmed for automatic electronic distribution of reports to the following individuals:

[insert list of CIP, Protocol, Cooperative Group & Other AE Notifications.
AdEERS provides a copy feature for other e-mail recipients]

[subsection numeral] Expedited Reporting Guidelines

*[**Select ONE** of the tables below (both are labeled 'A') and include WITH explanatory notes. **The first table** is to be used for agents that undergo **radioactive decay** such as labeled PET or SPECT agents. The **second table** should be selected for studies of **non-radioactive** imaging agents (e.g. MRI or US agents)]:*

ADEERS TABLE for REPORTING COMMERCIAL [Non-IND] AGENT EVENTS:

TABLE A *[use for radioactive imaging agents]*
All Phases
AdEERS Reporting Requirements for Adverse Events occurring within [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] Day(s) +/- 4 hours of the last use of a commercial agent[1]

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unex-pected	Expected	Unexpected	Expected
		with Hospital-ization	without Hospital-ization		with Hospital-ization	without Hospital-ization	with Hospital-ization	without Hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

1 Adverse events that occur more than [calculate and enter 10 Agent half-Lives rounded UP to the nearest whole day] day(s) after the last dose of agent and have an attribution of possible, probable, or definite require reporting as follows:

AdEERS 24-hour notification followed by complete report within 5 calendar days for-
- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report-
- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

TABLE A *[use for NON-radioactive imaging agents]*
All Phases
AdEERS Reporting Requirements for AEs occurring within 30 Days of the last use of a commercial agent[1]

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
		with Hospitalization	without Hospitalization		with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to agent administration or other cause must be provided.

1 **Adverse events that occur more than 30 days after the last dose of agent and have an attribution of possible, probable, or definite require reporting as follows:**

AdEERS 24-hour notification followed by complete report within 5 calendar days for-
- Grade 4 and Grade 5 Unexpected Events

AdEERS 10 calendar day report-
- Grade 3 Unexpected Events with Hospitalization
- Grade 5 Expected Events

[subsection numeral] Expedited AE reporting timelines defined:

- "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within 24 hours of learning of the event, followed by a complete AdEERS report within 5 calendar days of the initial 24-hour report.

- "10 calendar days" - A complete AdEERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.

Use the NCI protocol number and the protocol-specific patient ID assigned during trial

registration on all reports.

[subsection numeral] Protocol-Specific Expedited Adverse Event Reporting Exclusions

For this protocol only, certain AEs/grades are exceptions to the Expedited Reporting Guidelines and do not require expedited reporting (*i.e.*, AdEERS). The following AEs must still be reported through the routine reporting mechanism:

CTCAE Category	Adverse Event	Grade	Hospitalization/ Prolongation of Hospitalization	Attribution	Comments

[subsection numeral] Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions. **AEs reported through AdEERS must also be reported in routine study data submissions.**

[subsection numeral] Secondary AML/MDS

Investigators are required to report cases of secondary AML/MDS occurring on or following treatment on NCI-sponsored chemotherapy protocols using the NCI/CTEP Secondary AML/MDS Report Form. This form can be downloaded from the CTEP web site (http://ctep.cancer.gov). Refer to the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" (available at http://ctep.cancer.gov) for additional information about secondary AML/MDS reporting.