Dear Colleagues,

The updated Routine Adverse Event Reporting guidelines apply to legacy RTOG studies and current NRG Oncology studies for the following disease sites and the listed breast studies:

- Brain/CNS
- Head and Neck
- Lung
- Noncolorectal GI
- GU
- Sarcoma
- NRG-BR001
- NRG-BR002

For questions and concerns regarding the Routine Adverse Event Reporting guidance document and the applicable studies, please contact Sara McCartney.

Thank you,

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Guidance for routine Adverse Event reporting
(updated 5.11.2015):

Routine Adverse Event (AE) reporting falls under multidisciplinary purview, including data management, regulatory compliance, and statistics. An adverse event is “an untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related” (21 CFR Part 312). Routine AE reporting is an essential aspect of a safety monitoring program and this guidance document provides general instruction for the routine AE reporting process. For multi-modality RTOG studies, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug. This document does not usurp or replace protocol specific requirements related to adverse event reporting. Therefore, fastidious attention to unique protocol specifications is essential to ensure compliance with the protocol. In addition, this document reflects NRG Oncology adverse event reporting requirements only and does not supersede institutional requirements; you must be aware of and report adverse events according to your institutional policy.

- FDA regulations state clinical sites must record all non-serious AEs and report them to the sponsor according to the time table delineated in the protocol (21 CFR Part 312).

During protocol treatment and 30 days after end of treatment:
- Collection of AEs begins at the start of protocol treatment unless otherwise specified in the protocol
- As part of the pre-treatment, baseline physical assessment, comprehensive documentation of pre-existing and chronic adverse events in the patient medical record is part of an effective safety evaluation process in order to better ascertain if an event is exacerbated by the investigational treatment. Baseline, pre-existing AEs do not require reporting to NRG Oncology.
- All adverse events must be reported to NRG Oncology and documented in the patient’s medical record during protocol treatment and for 30 days after end of treatment.
  - Grade 1-5 events
  - Regardless of attribution
- All adverse events must be recorded on the appropriate case report form
- Adverse events are recorded until resolution
  - Continually record the AE on every subsequent CRF until resolution

During follow-up (greater than 30 days after end of protocol treatment):

Follow-up is defined as the period beginning 30 days after end of all components of protocol treatment. Refer to the protocol for variations and protocol-specific timeframes. Please note: if the patient experiences a delay in treatment greater than 30 days (e.g. to recover from toxicity, protocol-specified surgery, etc.) this is not considered follow-up.
• Continue to follow adverse events that occurred during study treatment plus 30 days after end of treatment but did not resolve by follow up timeframe.

• In order to evaluate duration of toxicity, follow and continually report all adverse events until resolution
  – In the event of AE chronicity, continually report the AE at the stable or current grade on the CRF for all subsequent reporting intervals during follow up
  – Actively query about the status of chronic AEs during each follow-up interval to assess for change in grade (intensity) over time and report accordingly. In the event of an increase in grade, record the start date for the new intensity of the AE.
  – See protocol for reporting expectations

• For adverse events that begin during the follow up time period, only report AEs reasonably related to the protocol treatment:
  – Possibly, probably, definitely
  – Grades 1-5

**Laboratory Test Values and Vital Signs**

Laboratory abnormalities and changes in vital signs (outside of reference range) are considered adverse events if they result in discontinuation or interruption of study treatment, are clinically significant and require therapeutic medical intervention, meet protocol specific criteria (see toxicity management in protocol) and/or if the investigator considers them to be adverse events. Laboratory values and vital signs that meet the criteria for a serious adverse event (SAE) should be reported in an expedited manner.

• Laboratory values and vital signs that are clearly attributable to another adverse event do not require discrete reporting (e.g. electrolyte disturbances in the context of dehydration, chemistry and hematologic disturbances in the context of sepsis, etc.)

All laboratory test results and vital signs captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported per expedited reporting procedures.

For questions please contact:

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