Southwest
Oncology Group
A National Clinical Research Group

August 1, 2006

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, UCOP AND AFFILIATE INVESTIGATORS AND CLINICAL RESEARCH ASSOCIATES - Also, please provide this information to your local Institutional Review Boards (IRBs)

FROM: The Southwest Oncology Group (SWOG)

RE: Office for Human Research Protections (OHRP) "Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others" and External Adverse Event Notification on Southwest Oncology Group protocols

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MEMORANDUM

This is to notify all investigators, clinical research staff and their designated IRBs participating in trials conducted by SWOG of important changes recently implemented in our procedures for processing and distributing Investigational New Drug (IND) safety reports of external adverse events. For the purposes of this memo, an external adverse event is defined as a report of an individual adverse event experienced by subjects enrolled in a clinical trial conducted by an entity other than SWOG - involving the same drug, but not necessarily under the same conditions (e.g., different doses, durations of therapy, diseases or subpopulations).

According to the draft Office for Human Research Protections (OHRP) "Guidance on Reporting and Reviewing Adverse Events and Unanticipated Problems Involving Risks to Subjects or Others" (October 2005), only a small proportion of "adverse events" that occur in patients being treated on an IRB-approved research protocol meet the criteria of being "unanticipated problems" that require reporting to local IRBs and Principal Investigators. The types of events that require such reporting under the HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) generally fall into the following three categories:

1) Adverse events that are serious, unexpected, and related or possibly related to participation in the research
2) Serious adverse events that are expected in some subjects, but are determined to be occurring at a significantly higher frequency or severity than expected
3) Other unexpected adverse events, regardless of severity, that may alter the IRB's analysis of the risk versus potential benefit of the research and, as a result, warrant consideration of substantive changes in the research protocol or informed consent process/document

It is one of the responsibilities of the IND sponsor for a study (the entity responsible for regulatory reporting to the U.S. Food and Drug Administration for that study) to determine which events meet the criteria outlined above and would require reporting to local IRBs. Additionally, in general, the IND sponsor and the scientific leadership for the trial are in the best position to perform an adequate assessment of serious adverse events. We recommend that all reports that we determine to meet the criteria below for distribution to institutions be reviewed by the responsible IRB. However, if the local IRB has specific, documented alternative processes for handling these reports (in the absence of associated protocol amendments), the local procedures will generally be accepted for the purposes of SWOG audits.

Specific changes to the SWOG procedures for review and distribution of external adverse event information:

In addition to the distribution of specific safety reports as outlined below, the FDA MedWatch listserver will be used as a primary resource for official FDA-approved labeling changes relating to safety information.

1. Safety reports involving investigational agents that are covered under an IND sponsored by SWOG (where the NCI does not hold an IND for that agent)

The Southwest Oncology Group will circulate to participating institutions only those individual adverse events and safety reports that we receive that meet either the first or third criterion listed above.

As a part of this process change, the Group's Protocol Coordinators will review all incoming SAE reports from external sources or reports referred via our internal SAE review and will determine if the report meets the protocol criteria for being "serious" and is at least "possibly related" and is "unexpected" (if the report does not meet all three criteria, it will not be distributed to the sites). If the Protocol Coordinator has any questions, he/she will consult with the Group's SAE Coordinator, Executive Officer (and the Study Coordinator, if needed). Additionally, if a report requires protocol modification based on internal SAE review or Study Coordinator review - it will be distributed to the participating sites along with the protocol amendment.

2. Safety reports involving investigational agents covered under an IND sponsored by NCI where the protocol in question is being performed under the NCI-IND for the agent.

In addition to reviewing SAE reports submitted on studies being performed under an IND sponsored by the NCI via the NCI's AdEERs system, physicians within the Investigational Drug Branch of CTEP currently conduct a central review of all IND safety reports issued by pharmaceutical collaborators of adverse events experienced by subjects enrolled in protocols not sponsored by CTEP. Individual case reports are sent in an expedited manner to investigators only when they are judged by the CTEP physician to be clinically meaningful. In the case of IND Safety Reports where no protocol changes are required, the report is scheduled for distribution to participating institutions in the next Group electronic broadcast of protocol documents. SWOG requires that these reports receive, at minimum, expedited IRB review at the sites no later than 90 days from the protocol posting.

3. Safety reports involving investigational agents covered under an IND sponsored by NCI where the protocol in question is being performed under a SWOG-IND for the agent.

SWOG will accept the NCI investigator's review and disposition of the IND Safety Reports if the study in question is included on the NCI's list for investigator distribution.

4. Safety reports involving agents covered under an IND sponsored by NCI where the protocol in question is being performed under IND-exempt status for the agent.

SWOG will review the NCI investigator's review and disposition of the IND Safety Reports to determine whether the event meets the criteria for requiring an update to the protocol document. SWOG will not routinely distribute safety reports for IND-exempt studies. However, the FDA MedWatch listserver will be used as a primary resource for official FDA-approved labeling changes relating to safety information. These will be distributed to the institutions and incorporated into the protocol document as applicable.

5. Safety reports where the protocol in question is being performed under IND-exempt status for the agent and there is no existing NCI-IND for the agent

SWOG will not routinely distribute safety reports for IND-exempt studies. However, the FDA MedWatch listserver will be used as a primary resource for official FDA-approved labeling changes relating to safety information. These will be distributed to the institutions and incorporated into the protocol document as applicable.

The role of the Group's Data and Safety Monitoring Committee and Study Committees

All studies will be monitored by either the Group's Data and Safety Monitoring Committee (DSMC) (for Phase III studies), or the protocol-specific Study Committee (for all other studies). Information regarding all reported toxicities on the study will be reported to sites, in the manner required by the study design, every six months in the Group's Report of Studies. When identified by the DSMC or Study Committee, increased frequency or severity of toxicity that has the potential for significantly altering the risk/benefit ratio will be reported to the participating sites immediately following the DSMC or Study Committee review.

Duration of Reporting Responsibilities

Unless there is a report of a serious new long-term toxicity (such as a secondary malignancy) which would require patient notification, all central distribution of safety reports from SWOG will end when all patients on a particular study have finished protocol treatment. IRB review responsibilities for routine safety reports end when all of the patients at the institutions for which the IRB is responsible have finished treatment.

cc: NCI – CTEP
Cooperative Groups – regulatory contacts
SWOG Headquarters Office
SWOG Statistical Center
SWOG Operations Office