Southwest
Oncology Group
A National Clinical Research Group

MEMORANDUM

TO: ALL SOUTHWEST ONCOLOGY GROUP MEMBER, CCOP, UCOP AND AFFILIATE INVESTIGATORS AND CLINICAL RESEARCH ASSOCIATES

FROM: SWOG Operations Office

DATE: April 15, 2008

SUBJECT: NCI/CTEP Memorandum of March 20, 2008 Regarding OHRP Regulations on Changes in Clinical Trial Informed Consent Documents and Continued Enrollment of New Participants

SWOG is providing its participating institutions with information that has been recently issued from the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI).

Please read the attached memorandum. The significance of the procedural change outlined in this memorandum relates primarily to the mechanism and timing for communication of new or modified risk information to new patients being enrolled on clinical research trials – for risk information that does not appear to significantly alter the risk-benefit profile for patients in these studies (i.e., represents no more than a minor alteration in the overall risk-benefit). In the past, CTEP's interpretation of the OHRP guidelines allowed for the continued enrollment of new patients after verbal communication of new risk information by physicians to their patients after notification of the information by the physician to the IRB, but prior to official IRB review and approval of this information in a protocol amendment. In this situation, it was considered acceptable that patients were verbally informed of the new risk information (and that this communication was documented in the patient record).

OHRP has indicated to CTEP that verbal communication of this type of new risk information in this manner to patients being newly enrolled on a clinical trial is not in compliance with OHRP regulations. New patients cannot be enrolled on a study until an amended protocol and informed consent document have been reviewed and approved by the designated IRB for that study. However, if the changes to the protocol and informed consent document represent no more than a minor alteration in the overall risk-benefit for patients, the amendment can undergo expedited review at the discretion of the Chair of the designated IRB. For those studies where the Central IRB is the IRB of record, the Chair of the Central IRB may also review such changes in an expedited fashion, at his/her discretion.

Expedited review of these documents, if granted by the Chair of the IRB of record, will be considered by CTEP and by SWOG to be sufficient review for this kind of change. SWOG will not suspend study registrations for these kinds of changes and, at the current time, will not require submission of IRB review for these protocol revisions via the CTSU Regulatory Support System. Institutions will be responsible for ensuring that they have met these requirements (and this information will be reviewed at the time of audit).

For those risk changes that either SWOG or the NCI designate as being major alterations in the overall risk-benefit ratio, the Group will centrally suspend registrations to the study and require submission of IRB approvals of these amendments via the CTSU Regulatory Support System before an institution may begin enrolling patients again. However, this is not a change from the way we have historically handled the kinds of changes.

CTEP has obtained OHRP concordance on the information in the attached CTEP memo.

Please do not hesitate to contact Dana Sparks, M.A.T. or Elaine Armstrong, M.S. in the Operations Office at 210/450-8808 if you have further questions.

PC/dbs

cc: Group Chair's Office staff
Statistical Center staff

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Cancer Institute
Bethesda, Maryland 20892

MEMORANDUM

DATE: March 20, 2008

TO: Cooperative Group Chairs, Cooperative Group Statisticians, Cooperative Group Administrators, and Consortia Principal Investigators

FROM: Jeff Abrams, MD, Acting Associate Director, CTEP, DCTD, NCI
Meg Mooney, MD, Acting Chief, Clinical Investigations Branch, CTEP, DCTD, NCI

SUBJECT: OHRP Regulations on Changes in Clinical Trial Informed Consent Documents and Continued Enrollment of New Participants

This memorandum is in reference to discussions between the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI), the Office of Human Research Protections (OHRP), and the Food and Drug Administration (FDA) regarding changes in informed consent documents in NCI/CTEP-sponsored clinical trials and the continued enrollment of new participants to those trials. OHRP has advised the NCI/CTEP staff that when new or modified risk information is discovered that requires an amendment to satisfy the requirements for informed consent under U.S. Department of Health and Human Services (HHS) regulations at 45 CFR 46.116(a)(2), enrollment of new participants must cease until the designated Institutional Review Board (IRB) has reviewed and approved the changes to the informed consent and protocol documents.

CTEP's procedures have been in compliance with OHRP regulations with respect to modifications to the informed consent and protocol documents for new or modified risk information for clinical oncology trials that it sponsors when the information represents a **major** alteration in the overall risk-benefit for new participants. In those situations, CTEP has required immediate suspension of accrual to the trial until an amendment that includes that information and a revised informed consent document is reviewed and approved by the IRB.

In situations in which new or modified risk information was considered to represent a **minor** alteration in the overall risk-benefit for new participants, CTEP's past procedures have not been in compliance with OHRP regulations. In those situations, CTEP allowed continued enrollment of new participants, before review and approval of a protocol amendment by the designated IRB, if the new information was verbally conveyed to new participants, the verbal communication was documented in the new participants' medical record, and the new participants signed a revised informed consent document once the appropriate IRB approved the protocol amendment.

In order to comply with OHRP regulations, CTEP has now revised its procedures to ensure that new or modified risk information that represents a minor alteration in the overall risk-benefit is conveyed to new participants appropriately. This information will be disseminated to sites participating in the clinical trial with an amended protocol and revised informed consent document. The sites will be instructed that new participants cannot be enrolled on the study until the amended protocol and informed consent document have been reviewed and approved by the designated IRB. However, since the changes to the protocol and informed consent document represent a minor alteration in the overall risk-benefit for participants, the participating sites will be notified that the amendment can undergo expedited review at the discretion of the Chair of the designated IRB (i.e., if the IRB Chair agrees that the new or modified risk information is minor with respect to the overall risk-benefit for participants in the trial, the Chair may review and approve the amendment via an expedited review procedure). Per NCI/CTEP's discussion with OHRP, expedited review by the IRB Chair in this situation would be in compliance with OHRP's interpretation of the regulations. New or modified risk information may be considered to represent a minor alteration in the overall risk-benefit for participants in oncology trials since participants enrolled on these trials already incur significant risks because of the potential lethality of their disease. Many treatment interventions in oncology are known to cause serious adverse events. If new or modified risk information provides additional detail on the risks of the treatment intervention under study without changing, in a major way, the overall weight given to the risks versus benefits for participants, a protocol amendment, including a revised informed consent document, containing this information may be subject to an expedited review procedure at the discretion of the IRB Chair.

cc: Michael A. Carome, MD, Associate Director for Regulatory Affairs, OHRP
James Doroshow, MD, Director, Division of Cancer Treatment and Diagnosis, NCI
Steve Friedman, MHSA, Acting Head, Protocol and Information Office, CTEP, DCTD, NCI
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