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Chairman

Clinical Coordinating Division
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To: NSABP Principal Investigators and Program Coordinators

From: Norman Wolmark, MD
Chair, NSABP Foundation, Inc.

Date: March 26, 2008

Re: **NCI/CTEP Policy Regarding Changes in Clinical Trial Informed Consent Documents
and Continued Enrollment of New Participants**

The NSABP is providing its Members with recently issued information from the Cancer Therapy Evaluation Program of the National Cancer Institute (CTEP/NCI) about important changes in procedures for patient enrollment following activation of study amendments that involve new or modified risk information. **This policy change will have an effect on patient accrual to oncology trials which could be substantial. It is vitally important that investigators review and understand the information in the attached CTEP policy letter as well as the decisions of their local institutional review boards (IRBs) on how to implement this policy locally.**

According to the Office of Human Research Protections (OHRP) interpretation of the U.S. Health and Human Services (HHS) regulations, when a protocol amendment involving any new or modified risk information is issued, new patients cannot be enrolled in studies **until** the designated IRB has reviewed and approved the changes to the informed consent and protocol documents. OHRP believes the regulations cannot be interpreted to provide a mechanism to allow for continued enrollment between the time of amendment activation by the Cooperative Group and IRB review. For many years, NCI and Cooperative Group policies have allowed *verbal discussion and consent* with prospective patients until IRB approval was obtained, when the new or modified information was considered a minor alteration in the overall risk-benefit ratio **and** when permitted by the local IRB. Cancer patients have potentially life-threatening disease and routinely receive therapies with potentially severe, life-threatening toxicities. An important component of clinical trials in oncology is the identification and quantification of toxicities associated with a new therapy so new toxicities that do not appreciably alter the overall risk/benefit ratio for patients are routinely identified in clinical trials. Because halting of accrual to ongoing trials has a substantial adverse effect on timely completion of accrual and presents participating sites with significant logistical challenges, the previous procedure allowed for accrual to continue while IRBs reviewed the new risk information.

However, from this date forward, issuance of **any** amendment with **any** new or modified risk information, or any amendment requiring full board review will result in **immediate** suspension of further accrual until the IRB of record has given approval for the amendment. As indicated in the attached document, CTEP has developed a procedure, in consultation with OHRP, to try to minimize the duration of accrual suspension following activation of amendments which contain new information that does not appreciably alter the risk/benefit ratio, referred to as **minor** alterations in the CTEP memo. If CTEP believes an amendment provides information that only results in a **minor** alteration, the Chair of the NCI Central IRB (CIRB) will be asked to provide an expedited review of the amendment. If the CIRB Chair agrees and gives expedited approval, the amendment will be activated by the NCI and the Cooperative Group based on the CIRB

approval. Thus, sites using the CIRB as their IRB of record will not experience a suspension of accrual. It is hoped that when local IRBs are the IRB of record, local IRB Chairs will follow the lead of the CIRB Chair and provide expedited approval so that the duration of accrual suspensions at these sites will be kept to a minimum. If the CIRB Chair gives expedited approval, but the local IRB Chair believes full board review is necessary, accrual will need to remain suspended at that site until the local IRB has completed its review and given approval of the amendment. If CTEP or the CIRB Chair believes the information in an amendment results in a major change in the risk/benefit ratio, accrual will be halted immediately by issuance of a formal Action Letter from CTEP. Accrual will not be resumed until the CIRB—and when applicable, the local IRB—have completed full board review and given approval.

We ask that investigators review this attached CTEP information thoroughly and discuss this policy with their IRBs. In order to minimize accrual suspensions as much as possible, investigators should understand their IRB's views and common practices regarding amendments. The NSABP and the other Cooperative Groups will be modifying future amendment instructions to align with the revised procedures of CTEP. Previously, for each amendment issued, the NSABP (and other Cooperative Groups) provided specific instruction about whether full board or expedited review would be acceptable. Moving forward, *in cases of minor alteration in the overall risk-benefit for new participants*, the determination of whether full board vs expedited review is required will be left to the local IRB. In order to comply with HHS regulations and to prevent citations on audit, investigators will need to ensure that patients are consented within designated timeframes (with respect to date of issuance of an amendment and IRB approval). Investigators who consent patients after an amendment is issued but before IRB approval is in place will receive a deviation upon audit and require a corrective action plan to ensure further compliance. **It is up to the local institution to ensure that patient accrual is suspended until IRB approval is in place.**

The changes in CTEP policy will have a profound effect on current systems and practices among the Cooperative Groups, and we anticipate that changes will evolve as different types of amendments are issued over the coming months. At this time, we do not have all the answers regarding how this will affect the processes that take place with CTEP, the CIRB, and the Cooperative Groups. The NCI has outlined plans and timelines to the Groups which will expedite the internal review process so that information is issued quickly; the details and iterations must undergo further discussion between CTEP and the Groups.

We hope to minimize prolonged accrual hiatuses that would severely affect patient participation in clinical trials. To do so will be a challenge in the current environment of requirements for risk notifications. We ask that you continue to work with us to ensure that trials are conducted safely and appropriately for oncology patients, and ask for your patience as we work on the details affected by the change in CTEP policy.

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



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 Doroshov, MD, Director, Division of Cancer Treatment and Diagnosis, NCI
Steve Friedman, MHSA, Acting Head, Protocol and Information Office, CTEP, DCTD, NCI
Joan Maurer, Chief, Clinical Trials Monitoring Branch, CTEP, DCTD, NCI
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