DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

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TO: Jeffrey Abrams, M.D.
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FROM: Acting Director, Office for Human Research Protections

SUBJECT: Institutional Review Board Review of Protocol and Informed Consent Changes

This memorandum is in reference to the recent discussions between the Cancer Therapy Evaluation Program (CTEP) at the National Cancer Institute (NCI) and the Office for Human Research Protections (OHRP) regarding the implementation of changes to protocols and informed consent documents for NCI/CTEP-sponsored clinical trials in a manner that satisfies the requirements of the Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46).

As you know, on March 20, 2008 CTEP issued a memorandum to NCI/CTEP-sponsored cooperative groups explaining implementation of revised CTEP procedures for handling amendments to cooperative group protocols and enrollment of new subjects in these protocols in situations in which new or modified risk information is considered to represent no more than a minor alteration in the overall risk-benefit relationship for subjects. On April 7, 2008 CTEP issued its first Action Letter under the revised CTEP procedures to investigators conducting CTEP/NCI-sponsored clinical trials involving the use of lapatinib (IND 70252). As we discussed, in response to the March 20 memorandum and the April 7 Action Letter, both OHRP and CTEP have received many inquiries from institutional review board (IRB) administrators and NCI/CTEP-sponsored cooperative group investigators expressing confusion about the following issues:

A. why the enrollment of new subjects must be suspended temporarily when CTEP identifies new or modified risk information that requires changes to the description of the reasonably foreseeable risks or discomforts in informed consent documents for NCI/CTEP-sponsored clinical trials;

B. whether the type of amendments referenced in the March 20, 2008 CTEP memorandum involving changes to the description of the reasonably foreseeable risks or discomforts in the protocol and informed consent documents based on the new or modified risk information could be eligible for IRB review under an expedited review procedure;

C. whether there are other types of changes to informed consent documents besides changes to the description of the reasonably foreseeable risks or discomforts that would require temporary suspension of new subject enrollment;

D. whether there are circumstances in which a decision is made to revise an informed consent document for an NCI/CTEP-sponsored clinical trial, but enrollment of new subjects does not need to be suspended pending IRB review and approval of the changes;

E. whether investigators need to get IRB approval before communicating new risk information to subjects already enrolled in NCI/CTEP-sponsored protocols;

F. whether investigators need to get IRB approval before implementing protocol changes affecting already enrolled subjects in NCI/CTEP-sponsored protocols; and

G. whether suspensions of new subject enrollment by CTEP pending IRB approval of protocol and informed consent document changes need to be reported to OHRP.

Given the apparent confusion by some IRB administrators and investigators regarding these issues, we would like to provide the following clarifications.

A. Temporary Suspension of New Subject Enrollment When CTEP Identifies New or Modified Risk Information that Requires Changes to the Description of the Reasonably Foreseeable Risks or Discomforts in Informed Consent Documents

For NCI/CTEP-sponsored clinical trials, informed consent must be documented by the use of a written consent form approved by the IRB and signed by the subject or the subject's legally authorized representative (45 CFR 46.117(a)). This written consent document must embody all elements of informed consent required by HHS regulations at 45 CFR 46.116(a) and (b), including a description of any reasonably foreseeable risks or discomforts to the subjects.

As we previously communicated to CTEP, when CTEP identifies or learns about new or modified risk information that necessitates changes to the description of the reasonably foreseeable risks or discomforts during the obtaining of informed consent in order to satisfy the requirements of HHS regulations at 45 CFR 46.116(a)(2) (or any other element of informed consent required under 45 CFR 46.116(a) or (b)), such changes to the informed consent documents, as well as any accompanying changes to the protocol, must be reviewed and approved by the IRB before the changes are initiated, except when necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)(iii) and 46.117). In these circumstances, new subjects cannot be enrolled until revised informed consent documents, and any proposed changes to the protocol, have been reviewed and approved by the IRB.

These regulatory requirements provide two important protections for human subjects. First, the IRBs can determine whether or not the requirements of HHS regulations at 45 CFR 46.111 are still met in light of the new risk information. In particular, the IRB must determine whether or not risks to subjects are minimized and whether or not risks to subjects are reasonable in relation to anticipated benefits (45 CFR 46.111(a)(1) and (2)). The second protection is for the IRB to review the way in

which the information is provided to prospective subjects to ensure that it is in language understandable to the subject and that it accurately presents the new risk information.

B. Changes to the Descriptions of the Reasonably Foreseeable Risks or Discomforts in the Protocol and Informed Consent Documents: Eligibility for IRB Review Under an Expedited Review Procedure

Under HHS regulations at 45 CFR 46.110, an IRB may use an expedited review procedure to review minor changes in previously approved research during the period (of one year or less) for which approval is authorized. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among the members of the IRB. OHRP notes that the HHS regulations do not define the meaning of *minor*, and as a result, IRBs have significant latitude in setting the parameters for what changes to research are considered minor. Determining whether or not a particular change to a research protocol or informed consent document is minor should take into consideration the nature of the previously approved research and the content of the previously approved protocol and informed consent documents.

It is our view that it is appropriate for CTEP to provide in its Action Letters the following:

(1) its opinion as to whether the changes proposed in the Action Letter in response to new or modified risk information are minor and therefore eligible for expedited review; and

(2) its expert assessment regarding whether the new or modified risk information adversely impacts the overall risk-benefit relationship for the subjects of the research and therefore may significantly alter the prior determinations of the IRBs required for approval of research under HHS regulations at 45 CFR 46.111 (in particular, the determinations under 45 CFR 46.111(a)(1) and (2)).

When CTEP determines that the proposed changes are minor, these changes may be reviewed by the IRB under an expedited review procedure *if the IRB chairperson (or another experienced IRB member designated to conduct expedited review by the chairperson) concurs with CTEP's assessment*. If the IRB chairperson (or designee) does not concur with CTEP's assessment that the changes are minor, the changes must then be reviewed at a convened meeting of the IRB.

In addition, regardless of whether the changes are reviewed by the IRB under an expedited review procedure or at a convened meeting, the IRB must determine whether or not the requirements of HHS regulations at 45 CFR 46.111 are still met in light of the new risk information. In making these determinations, the IRB may consider CTEP's assessment of whether the new or modified risk information adversely impacts the overall risk-benefit relationship for the subjects of the research.

We note that it is important for CTEP and IRBs evaluating changes proposed in a CTEP Action Letter to distinguish between the newly discovered information about research risks and the changes that are proposed in response to that new risk information. Having carefully reviewed several of the most recently issued CTEP Action Letters, we note that the changes typically proposed in such letters are intended to inform investigators, IRBs, and subjects about the previously unrecognized

risks and to implement procedures that will decrease those risks (e.g., by revising the inclusion or exclusion criteria or by implementing additional safety monitoring procedures).

We encourage IRBs to develop mechanisms whereby minor changes to protocol and informed consent documents, deemed appropriate for review under an expedited review procedure, receive prompt and timely review so that study enrollment may proceed with minimal interruptions.

C. Other Types of Changes to Informed Consent Documents Besides Changes to the Description of Risks that Would Require Temporary Suspension of New Subject Enrollment

When CTEP or investigators conducting CTEP/NCI-sponsored clinical trials identify or learn about new information that necessitates changes to the description of any other element of informed consent required under HHS regulations at 45 CFR 46.116(a) or (b), such changes to the informed consent documents, as well as any accompanying changes to the protocol, must be reviewed and approved by the IRB before the changes are initiated, except when necessary to eliminate apparent immediate hazards to subjects (45 CFR 46.103(b)(4)(iii)). In these circumstances, new subjects cannot be enrolled until revised informed consent documents, and any proposed changes to the protocol, have been reviewed and approved by the IRB. Some examples of such changes other than changes to the description of reasonably foreseeable risks or discomforts include the following:

(1) CTEP investigators note that the IRB-approved informed consent document for a clinical trial does not include a description of one of the research procedures (e.g., a procedure to obtain blood samples from subjects and perform a test for a genetic marker that is being assessed as a predictor of tumor responsiveness to the chemotherapy interventions being tested in the clinical trial) and determine that the informed consent document needs to be amended to include a description of this procedure so that it satisfies the requirements of 45 CFR 46.116(a)(1).

(2) CTEP determines that the IRB-approved informed consent document for a clinical trial includes a description of benefits to the subjects that overestimates the likely benefits of the research for subjects and requires that the benefits section be amended accordingly so that it satisfies the requirements of 45 CFR 46.116(a)(2).

(3) CTEP investigators note that there is an additional alternative course of treatment that is available outside of the research and may be advantageous to the subjects, but is not described in the IRB-approved informed consent document for a clinical trial, and determines that this additional alternative needs to be added to the informed consent document so that it satisfies the requirements of 45 CFR 46.116(a)(4).

D. Proposed Changes to Informed Consent Documents that do not Require Temporary Suspension of Subject Enrollment

We note that sometimes CTEP or investigators conducting NCI/CTEP-sponsored clinical trials decide to make changes to informed consent documents for clinical trials, including changes to how risk information is presented, that are not necessary for the informed consent to satisfy the requirements of 45 CFR 46.116. In these circumstances, it is not necessary for investigators to suspend enrollment of

new subjects until a revised informed consent document is reviewed and approved by the IRB. Therefore, subject enrollment may continue before the IRB reviews and approves such changes in the informed consent documents. However, keep in mind that revisions to the informed consent document cannot be implemented until they are approved by the IRB. Examples of proposed changes to informed consent documents that would not require temporary suspension of subject enrollment include the following:

(1) The IRB-approved informed consent document for a clinical trial includes the risk of "nausea," and CTEP decides to seek IRB approval to change this to the risk of "nausea or stomach upset" at the time of the next continuing review, even though all prospective subjects are expected to be able to understand the meaning of the work "nausea." In this case, the currently approved informed consent document still accurately reflects this risk.

(2) Changes that provide additional specific details of a risk that already is described in the IRB-approved informed consent document. For example, the IRB-approved informed consent document for a clinical trial describes the risk of "developing abnormal heart rhythms, some of which may result in death," and CTEP decides to revise the informed consent document to describe the risk of "developing abnormal heart rhythms, some of which may result in death such as ventricular tachycardia and ventricular fibrillation."

(3) Changes indicating that the probability of a specific adverse event occurring is lower than or slightly higher (i.e., no more than a few percentage points) than the probability stated in the IRB-approved informed consent document. For example, dizziness is included in the IRB-approved informed consent document with the stated probability occurrence being 10% of subjects, and based upon new risk information, this probability of occurrence is going to be changed to less than 1% of subjects or to 12% of subjects.

(4) Changes indicating that the level of severity of a specific adverse event is lower than the level of severity described in the IRB-approved informed consent document. For example, the IRB-approved informed consent document for a clinical trial describes the risk of developing severe anemia, and based on new risk information, CTEP plans to revise the informed consent document to describe the risk of mild anemia.

<u>E. Communication of New Risk Information to Subjects Already Enrolled in a Clinical Trial Without Obtaining IRB Approval</u>

We note that HHS regulations at 45 CFR 46.116(b)(5) state that when appropriate, informed consent should include a statement that significant new findings developed during the course of the research that may relate to a subject's willingness to continue participation will be provided to the subject. In most cases for NCI/CTEP-sponsored clinical trials, inclusion of this statement in the informed consent document would be appropriate. HHS regulations at 45 CFR 46.115(a)(7) also require that an institution, or when appropriate an IRB, shall maintain adequate documentation of IRB activities, including statements of significant new findings provided to subjects, as required by 45 CFR 46.116(b)(5). When HHS issued its revised final rule amending 45 CFR part 46 on January 26, 1981, it stated the following:

> "The requirement for IRB approval of new information provided to the subject during the course of research is removed from the final regulations. Information on significant new findings which is given to the subject shall be reported to the IRB, as required by § 45.115." [46 FR 8384]

Therefore, there is no requirement for IRB review and approval of such statements before they are provided by investigators to already enrolled subjects. We suggest that IRBs have procedures in place to review the research in light of the significant new findings to determine if modifications are needed.

It is our view that the type of new risk information typically described in CTEP Action Letters may reasonably be considered to represent significant new findings developed during the course of research that may relate to a subject's willingness to continue participation. When this is the case, CTEP may advise investigators to (1) communicate such new risk information promptly to already enrolled subjects, and (2) provide IRBs with copies of such statements of significant new findings.

F. Implementing Protocol Changes Affecting Subjects Already Enrolled in a Clinical Trial Prior to Obtaining IRB Approval

As noted above, CTEP Action Letters frequently propose changes to research protocols that include implementation of procedures intended to decrease risks to the subjects, such as implementing additional safety monitoring procedures. For already enrolled subjects, it may be appropriate to implement such procedures immediately in order to limit potential immediate harms to subjects. As noted above, the HHS regulations at 45 CFR 46.103(b)(4)(iii) do permit investigators to initiate changes in IRB-approved research without first obtaining IRB approval when doing so is necessary to eliminate apparent immediate hazards to the subjects. Therefore, when CTEP believes that investigators should implement new safety monitoring procedures to limit potential immediate harms to already enrolled subjects, it may advise investigators to do so prior to their obtaining IRB approval for such changes.

G. Suspensions of New Subject Enrollment by CTEP Need Not be Reported to OHRP

When CTEP issues an Action Letter directing CTEP investigators to suspend enrollment of new subjects into a clinical trial until the IRB approves changes to the protocol or the informed consent document, institutions engaged in the clinical trial do not need to submit a report of the suspension to OHRP because such a suspension does not represent a suspension of IRB approval of the research. However, if the IRB subsequently suspends its approval of the research, such a suspension would need to be reported to OHRP by the institution.

We note that in some cases, new risk information that leads to the changes may represent an unanticipated problem involving risks to subjects that needs to be promptly reported to the IRB, appropriate institutional officials, and OHRP. In such cases, we would expect CTEP to indicate in its Action Letter that the new risk information represents an unanticipated problem involving risks to subjects and to report the problem to OHRP on behalf of all institutions engaged in the pertinent

clinical trial (see OHRP's guidance on reviewing and reporting unanticipated problems involving risks to subjects or others and adverse event on our website at http://www.hhs.gov/ohrp/policy/AdvEvntGuid.pdf).

We hope these clarifications are helpful to CTEP and provide a mechanism for addressing the apparent confusion expressed by some members of the IRB and research communities regarding the above issues.

Please let me know if you have any questions regarding this matter.

/S/

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