DEPARTMENT OF HEALTH & HUMAN SERVICES

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October 3, 2000

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RE: Human Research Subject Protection Under Multiple Project Assurance (MPA) M-1011

Research Projects: Research Conducted under Eastern Cooperative Oncology Group (ECOG) and National Surgical Adjuvant Breast and Bowel Project (NSABP) protocols

Dr. Dang and Mr. Peterson:

The Office for Human Research Protections (OHRP), formerly the Office for Protection from Research Risks (OPRR), has reviewed Dr. Bart Chernow's April 23, June 30, and October 23, 1998 letters regarding the above referenced research that were submitted in response to OPRR's letter of March 3, 1998. OHRP apologizes for the delay in its response.

Based upon its review of the materials submitted by Dr. Chernow, OHRP finds that the Johns Hopkins University School of Medicine (JHUSM) developed satisfactory corrective action plans to address the following deficiencies referenced in OPRR's March 3, 1998 letter: (i) inappropriate use of expedited review by the Institutional Review Board (IRB) for continuing review of some oncology clinical trials; (ii) lack of timely continuing review of some oncology clinical trials by the IRB; (iii) lack of continuing review by the IRB for some oncology clinical

trials for which subject accrual was complete, but subjects were still followed for collection of survival data; and (iv) lack of complete disclosure of all reasonably foreseeable risks in the IRB-approved informed consent documents for some oncology clinical trials.

As a result of the above determination, there should be no need for further involvement of OHRP in the above referenced matters. However, JHUSM must notify OHRP promptly of any new information that might alter this determination.

Assessment of Written IRB Policies and Procedures

OHRP has reviewed the written IRB policies and procedures that were submitted with Dr. Chernow's April 23, 1998 letter, as well as those that are currently posted on the JHUSM internet web page. Based upon its review, OHRP is concerned that the written IRB policies and procedures fail to adequately describe the following activities, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4) and (5):

> (1) The procedures which the IRB follows for conducting its continuing review of research.
>
> (2) The procedures which the IRB follows for reporting its findings and actions regarding initial and continuing review to the institution.
>
> (3) The procedures which the IRB follows for determining which projects require review more often than annually.
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> (4) The procedures which the IRB follows for determining which projects need verification from sources other than the investigators that no material changes have occurred since the previous IRB review.
>
> (5) The procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, the head of any supporting Federal Department or Agency, and OHRP of each of the following events:
>
> > (a) Any unanticipated problems involving risks to subjects or others.
> >
> > (b) Any serious or continuing noncompliance with the requirements of 45 CFR Part 46, or the requirements or determinations of the IRB.
> >
> > (c) Any suspension or termination of IRB approval of research.

OHRP requests that you submit a written response to the above concern with your report due October 31, 2000 regarding the research activities referenced in OHRP's September 21, 2000

letter. This response should include revised written IRB policies and procedures that provide the operational details for each of the above referenced IRB procedures.

Guidance on Written IRB Policies and Procedures

In order to assist JHUSM in the evaluation and revision of its written IRB policies and procedures, OHRP provides the following guidance:

(1) Written IRB policies and procedures should specify the documents and materials that are provided to primary reviewers (if any) and all other IRB members prior to the IRB meetings for protocols undergoing initial or continuing review.

(2) In conducting the initial review of proposed research, IRBs must obtain information in sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111. Materials should include the full protocol, a proposed informed consent document, any relevant grant applications, the investigator's brochure (if one exists), and any advertising intended to be seen or heard by potential subjects. Unless a primary reviewer system is used, all members should receive a copy of the complete documentation. These materials should be received by members sufficiently in advance of the meeting date to allow review of this material.

(3) Convened IRBs often set conditions under which a protocol can be approved (OHRP discourages use of the term "Conditional Approvals"). The following guidelines apply in such cases: (a) when the convened IRB requests substantive clarifications, protocol modifications, or informed consent document revisions, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material; (b) only when the convened IRB stipulates specific revisions requiring simple concurrence by the investigator may the IRB Chairperson or designated reviewer subsequently approve the research on behalf of the IRB.

(4) Continuing IRB review of research must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, all IRB members should at least receive and review a protocol summary and a status report on the progress of the research, including (a) the number of subjects accrued; (b) a description of any adverse events or unanticipated problems involving risks to subjects or others and of any withdrawal of subjects from the research or complaints about the research; (c) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, reports on multi-center trials and any other relevant information, especially information about risks associated with the research; and (d) a copy of the current informed consent document. Primary reviewer systems may be employed, so long as the full IRB receives the above information. Primary reviewers should also receive a copy of the complete protocol including any modifications previously approved by the IRB (see OPRR Reports 95-01). Furthermore,

the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB.

When conducting research under an expedited review procedure, the IRB Chair (or designated IRB member(s)) should receive and review all of the above referenced documentation.

(5) IRB protocol records must include all the information stipulated at 45 CFR 46.115(a)(1),(3),(4),(7). The minutes of IRB meetings must include all the information stipulated at 45 CFR 46.115(a)(2).

(6) OHRP recommends that documentation for initial and continuing reviews conducted utilizing expedited review procedures include the specific permissible categories (see 63 FR 60364) justifying the expedited review.

(7) OHRP strongly recommends that IRB members absent themselves from the meeting room when the IRB votes on research in which they have a conflicting interest [see 45 CFR 46.107(e)], and such should be noted in the IRB meeting minutes.

(8) IRBs must determine which protocols require continuing review more often than annually, as appropriate to the degree of risk [see 45 CFR 46.103(b)(4) and 46.109(e)]. OHRP recommends that the minutes of IRB meetings clearly reflect these determinations regarding risk and approval period (review interval) for each protocol that is approved.

(9) OHRP recommends that each revision to a research protocol be incorporated into the written protocol. This practice ensures that there is only one complete protocol with the revision dates noted on each revised page and the first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents which then supersede the previous one.

(10) Regarding the CLINICAL INVESTIGATION CONSENT FORM sample language:

> (a) An explanation of whom to contact for "questions about research subjects' rights" should be added, as required by HHS regulations at 45 CFR 46.116(a)(7).
>
> (b) The section entitled "JOINING OF YOUR FREE WILL" should be modified to indicate that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, as required by HHS regulations at 45 CFR 46.116(a)(8). Simply stating that "All normal treatment options will still be available to you [if you decide not to participate]" is not sufficient.
>
> (c) OHRP strongly recommends that the additional elements of informed consent stipulated by HHS regulations at 45 CFR 46.116(b) be incorporated into the

sample informed consent document with instructions to include each when appropriate.

(11) Regarding the IRB policy for EMERGENCY APPROVAL PROCEDURES, please note that the following guidance applies to all Federally supported research activities, and in accordance with the JHUSM MPA, should apply to all research, regardless of sponsorship:

> HHS regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval (see 45 CFR 46.103(b), 46.116(f) and OPRR Reports 91-01). When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a research activity. When emergency care involves investigational drugs, devices, or biologics, U.S. Food and Drug Administration (FDA) requirements must be satisfied.

(12) Regarding the policy on research involving prisoners, please see the enclosed May 19, 2000 OPRR memorandum for additional guidance on approving research involving prisoners

OHRP appreciates the commitment of your institution to the protection of human research subjects. Please contact me if you have any questions regarding this matter.

Sincerely,

Michael A. Carome, M.D.
Director, Division of Compliance Oversight

Enclosures: (1) OPRR Reports 95-01
(2) OPRR Reports 91-01
(3) May 19, 2000 OPRR memorandum regarding prisoner research

cc: Ms. Barbara L. Starklauf, Adminstrator, Human Subjects Committees, JHUSM
Dr. Sue K. Donaldson, Dean, School of Nursing, JHU
Dr. Jacquelyn Campbell, School of Nursing, JHU
Mr. George F. Schaeffer, President, The Johns Hopkins Bayview Medical Center (JHBMC)
Dr. Gary Briefel, M.D., Chair, JHBMC IRB (IRB-02)
Dr. Thomas R. Hendrix, Chairman, JCCI (IRB-01), JHUSM
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cc (continued):

Dr. Gary W. Goldstein, President, Kennedy Krieger Institute
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