DEPARTMENT OF HEALTH & HUMAN SERVICES

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Mr. John M. Allen
Assistant Vice President for Scientific Affairs
Office of Scientific Affairs
State University of New York
Health Science Center at Brooklyn
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RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1073

Dear Mr Allen:

The Office for Human Research Protections (OHRP) has reviewed your August 17, 2000 letters that were submitted in response to OHRP's July 17, 2000 letter regarding human subject protections at the State University of New York Health Science Center at Brooklyn (SUNY-HSCB).

OHRP acknowledges that your letters adequately respond to the concerns and questions raised in OHRP's July 17, 2000 letter. As a result, OHRP is closing its compliance oversight evaluation of SUNY-HSCB.

At this time, OHRP provides the following additional guidance and recommendations:

(1) In conducting the initial review of proposed research, the Institutional Review Boards (IRB) 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.

(2) If the IRB uses a primary reviewer system, the primary reviewer(s) should do an in-depth review of all pertinent documentation. All other IRB members should at least receive and review a protocol summary (of sufficient detail to make the determinations required under HHS regulations at 45 CFR 46.111), the proposed informed consent document, and any advertising material. In addition, the complete documentation should be available to all members for review.

(3) Continuing IRB review is required as long as individually identifiable follow-up data are collected on subjects enrolled in HHS-supported Cooperative Protocol Research Program (CPRP) protocols. This remains the case even after a protocol has been closed at all sites and protocol-related treatment has been completed for all subjects.

(4) OHRP notes that IRBs frequently approve research contingent upon substantive modifications or clarifications without requiring additional review by the convened IRB. OHRP recommends the following guidelines 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 Chair or another IRB member designated by the Chair subsequently approve the revised research protocol on behalf of the IRB under an expedited review procedure.

(5) Where Department of Health and Human Services (HHS) regulations require specific findings on the part of the IRB, such as (a) approving a procedure which alters or waives the requirements for informed consent [see 45 CFR 46.116(d)]; (b) approving a procedure which waives the requirement for obtaining a signed consent form [see 45 CFR 46.117(c)]; (c) approving research involving prisoners (see 45 CFR 46.305-306); or (d) approving research involving children (see 45 CFR 46.404-407), the IRB should document such findings. OHRP strongly recommends that all required findings be fully documented in the IRB minutes, including protocol-specific information justifying each IRB finding. If the SUNY-HSCB IRBs elect not to document these findings in the minutes, they should document them elsewhere in the IRB records.

(6) OHRP notes that on December 15, 1999, the SUNY-HSCB IRB (Committee B) approved a research project involving prisoners as subjects (i.e., protocol # 99-039) that apparently was supported by the National Institute of Mental Health. OHRP calls to your attention the following HHS regulatory requirements for research involving prisoners as subjects (see additional detailed guidance at http://ohrp.osophs.dhhs.gov/humansubjects/guidance/prison.htm):

> (a) HHS regulations at 45 CFR 46.304 require modification of IRB membership for review of research involving prisoners as subjects. In specific, at least one member of the IRB shall be a prisoner, or a prisoner representative with appropriate background and experience to serve in that capacity. When the convened IRB reviews research involving prisoners (including initial review,

continuing review, review of protocol modifications, and review of unanticipated problems involving risks to subjects or others), the prisoner or prisoner representative must be present as a voting member. Furthermore, the IRB membership rosters submitted to OHRP under your MPA should identify the prisoner(s) or prisoner representative(s). OHRP notes that IRBs frequently include as prisoners representatives individuals whose background and experience is insufficient for representing the prisoner's perspective.

(b) HHS regulations at 45 CFR 46.305(a) require that the IRB make seven specific findings whenever it approves research involving prisoners as subjects.

(c) HHS regulations at 45 CFR 46.305(c) and 306(a)(1) require that for HHS-supported research involving prisoners as subjects, the institution conducting the research must certify to the Secretary of HHS (OHRP) that the IRB has fulfilled its duties under HHS regulations at 45 CFR 46.305(a).

(d) Prior to conducting any HHS-supported research involving prisoners as subjects, institutions must await written confirmation from OHRP that it concurs with the IRB's finding made under HHS regulations at 45 CFR 46.305(a) and has determined that the proposed research falls within one of the categories of permissible research specified under 45 CFR 46.306(a)(2).

OHRP emphasizes that any HHS-supported research involving prisoners as subjects being conducted by SUNY-HSCB should be suspended unless all of the above regulatory requirements have been satisfied. The written certifications referenced above should be submitted to OHRP's Ms. Elyse Summers.

(7) HHS regulations at 45 CFR 46.103(f) require that an institution with an approved assurance shall certify that each *application* for research has been reviewed and approved by the IRB. In accordance with this regulatory requirement the IRB must receive and review a copy of all Federal grant applications involving human subject research. This review may be conducted by a primary reviewer.

(8) 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.

(9) 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.

(10) 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.

(11) OHRP recommends that institutions adopt policies describing the types of minor changes in previously approved research which can be approved by expedited review in accordance with HHS regulations at 45 CFR 46.110(b)(2).

(12) In accordance with the requirements of HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) and the SUNY-HSCB MPA, each of the following events must be promptly reported to the IRB, appropriate institutional officials, OHRP, and any supporting Federal department of agency, if applicable:

(a) Any unanticipated problems involving risks to subjects or others.

(b) Any serious or continuing noncompliance with 45 CFR Part 46 or the requirements or determinations of the IRB.

(c) Any suspension or termination of IRB approval.

OHRP notes that in accordance with the SUNY-HSCB MPA, such reporting must be satisfied for all research, regardless of sponsorship.

(13) The SUNY-HSCB IRB policies and procedures should be expanded to include the following:

(a) A description of 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.

(b) A detailed description of the IRB procedures for reporting its findings and actions to the investigator.

(c) A detailed description of the IRB procedures for determining which projects require review more often than annually.

(d) A detailed description of the IRB procedures for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(e) A detailed description of the IRB procedures for ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazards to the subject.

Please note that OHRP anticipates that it will conduct a compliance oversight site visit to SUNY Brooklyn within the next 12-24 months in order to assess SUNY-Brooklyn's system for protection of human subjects and its implementation of HHS regulatory requirements and OHRP's guidance.

OHRP appreciates your institution's commitment to the protection of human subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Sanford Leikin, M.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

Enclosure: OPRR Reports 95-01

cc: Dr. Greg Koski, OHRP
Dr. Melody Lin, OHRP
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