DEPARTMENT OF HEALTH & HUMAN SERVICES

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May 31, 2001

Kenneth L. Dretchen, Ph.D.
Director, Office of Regulatory Affairs
Georgetown University
3900 Reservoir Road, N.W.
NW103 Medical-Dental Building
Washington, D.C. 20007

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1255

Research Project: Race and Gender Differences in Clinical Decision Making
IRB Project Number: 113-94
HHS Project Number: R01 HS07135
Principal Investigator: Kevin Schulman, M.D.

Dear Dr. Dretchen:

The Office for Human Research Protections (OHRP) has reviewed your report of May 10, 2001, regarding the above referenced research project conducted by Georgetown University (GU).

OHRP Findings and Concerns Regarding IRB Project Number 113-94

Based upon its review of the documents provided with your report, OHRP makes the following determinations regarding the above referenced research project:

(1) HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. OHRP finds that the IRB did not

review and approve changes in the remuneration for the subjects enrolled in the above-referenced protocol.

Corrective Action: OHRP acknowledges that the GU IRB is revising its protocol review and continuing review forms to request such information, and that investigators will be reminded that all incentives offered to subjects must be approved by the IRB. By July 23 please provide OHRP with copies of the revised forms.

(2) OHRP finds that the recruitment practices for this project were not fully reviewed and approved by the IRB in accordance with HHS regulations at 45 CFR 46.111(a)(4), as well as GU policy requiring the IRB to review any direct advertising for research subjects. In specific, the recruitment postcard sent to prospective physician subjects was not reviewed and approved by the IRB.

Corrective Action: OHRP acknowledges that the GU IRB has put into place enhanced policies and forms to ensure that recruitment issues are fully considered and documented by the IRB. By July 23 please provide OHRP with copies of the revised forms.

OHRP has the following additional questions and concerns regarding the above-referenced research:

(3) HHS regulations at 45 CFR 46.109(a) require that the IRB review and approve all non-exempt human subject research. OHRP remains concerned that the IRB failed to review and approve the research involving medical students that was described in the following abstracts and manuscript:

(a) Tinoco A, Lenert L, Escarce J, Harless W, Schulman K. Impact of patient race and gender on perceived utility for health states (abstract). *Medical Decision Making*. 1996; 16:466.

(b) Rathore SS, Lenert LA, Weinfurt KP, Tinoco A, Taleghani CK, Harless W, Schulman KA. Bias in medical students: effect of patient race and gender on perceived health values (abstract). *Medical Decision Making*. 1998;17:I-479.

(c) Rathore SS, Lenert LA, Weinfurt KP, Tinoco A, Taleghani CK, Harless W, Schulman KA. Medical students and bias: race, gender and patient evaluations. Submitted to the *American Journal of Medicine*.

Given that IRB protocol number 113-94 did not include procedures described in the abstracts and manuscript, specifically (i) randomization of medical students to different experimental groups; and (ii) deception of such subjects, OHRP is concerned that the research activities described in the abstracts and manuscript were a major deviation from the IRB-approved protocol. Although the principal investigator requested approval to distribute a flyer and e-mail advertisement for protocol number 113-94 to medical

students at GU, appropriate changes **to the protocol** were apparently not reviewed and approved by the IRB. HHS regulations at 45 CFR 46.103(b)(4)(iii) require that the IRB review and approve all proposed changes in a research activity, during the period for which IRB approval has already been given, prior to initiation of such changes, except when necessary to eliminate apparent immediate hazards to the subjects. These events suggest that the IRB Chair failed to conduct an appropriate review of the proposed advertisement to ensure that it was consistent with the IRB-approved protocol.

Please respond **in detail**. In your response, please provide a copy of the IRB-approved protocol, if any, that included randomization of medical students and the assessment of racial and gender bias in clinical decision making by medical students.

OHRP Findings, Concerns and Guidance Regarding GU's Systemic Protections for Human Subjects

(4) Department of Health and Human Services (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 Institutional Review Board (IRB). OHRP finds that until 1993 the GU IRB failed to review grant applications for each proposal submitted.

Corrective Action: OHRP acknowledges that the IRB receives and reviews copies of complete grant applications proposing human subject research that are submitted for Federal support since 1993. OHRP finds that this corrective action adequately addresses the finding and is appropriate with GU's Multiple Project Assurance.

(5) OHRP finds that the written IRB policies and procedures submitted with your report fail to adequately describe the following activities, as required by Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) and 46.103(b)(4) and (5):

(a) The procedures which the IRB will follow for conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the institution.

(b) The procedures which the IRB will follow for determining which projects require review more often than annually.

(c) The procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review.

(d) The procedures which the IRB will follow 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.

(e) 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:

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

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

(iii) Any suspension or termination of IRB approval.

In addition, HHS regulations at 45 CFR 46.116(a)(8) require that informed consent include a statement that ". . . refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled. . . ." The GU model informed consent document states that "Refusal to participate. . .will not harm an individual's relationship with the investigators, his/her physicians, the hospital or the University." Since there could be penalties or loss of benefits other than harm to the individual's relationship with the University or its employees, OHRP finds that this language does not satisfy the requirements of HHS regulations at 45 CFR 46.116(a)(8).

Corrective Action: OHRP acknowledges that IRB GU is in the process of rewriting its policy and procedures manual and model informed consent document with the help of consultants. By July 23, please provide OHRP with a copy of the revised manual and forms.

(6) HHS regulations at 45 CFR 46.404-407 require specific findings on the part of the IRB for approval of research involving children. OHRP is concerned that the IRB may not consistently make the required findings when reviewing research involving children. For example, the minutes of IRB meetings for the following research protocols do not include the required findings: 00-312, 01-007, 01-049, and 01-053. Please respond.

(7) OHRP is concerned that the IRB approved protocol number 00-315 contingent upon substantive modifications or clarifications (the IRB questioned the likelihood that the sample size would be sufficient to detect differences between groups) 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 should 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.

(8) HHS regulations at 45 CFR 46.116 prohibit any exculpatory language in written or oral informed consent through which the subject is made to waive, or appear to waive, any of the subject's legal rights. OHRP is concerned that the following language in the IRB-approved informed consent documents appears to be exculpatory: "...you waive any claim of [company], Georgetown University, Georgetown University Hospital or their affiliates for any such compensation or any property interest in any such developments." (protocol number 00-175); "By signing this consent form, you waive any claim to be compensated ...and you give up any claim to property rights of these tissues." (protocol number 00-310); "...waiving any claim for compensation and any property interest in the samples." (protocol number 00-317). Please respond.

(9) HHS regulations at 45 CFR 46.116(a)(4) require the following element in informed consent documents: A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject. In discussion of protocol number 01-007, the IRB appeared to conclude that the informed consent document need only include "what the standard of treatment is" and no other options besides the research. OHRP is concerned that this does not sufficiently meet the requirements of 45 CFR 46.116(a)(4). Please respond.

(10) The IRB's discussion of several protocols (protocol numbers 01-036 and 01-035) stated that since the protocols only involved "competent" or "sound" adults, that there were no vulnerable subjects. OHRP is concerned that the IRB does not apparently appreciate that there are other categories of vulnerable subjects. HHS regulations at 45 CFR 46.111(b) require the IRB to ensure that additional safeguards have been included in research to protect the rights and welfare of vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled person, or economically or educationally disadvantaged persons. Please respond.

(11) HHS regulations at 45 CFR 46.107(e) stipulate that no IRB member may participate in the IRB's initial or continuing review of a project in which the member has a conflicting interest, except to provide information requested by the IRB. OHRP is concerned that an IRB member inappropriately participated in the initial and continuing review of a protocol for which he or she apparently had a conflicting interest because of possible involvement in the research (primary reviewer of 01-041 on February 1, 2001). The minutes indicate that the IRB did not think that this investigator's involvement in the research constituted a conflict "because the reviewer did not personally hold a financial interest." There can be other conflicting interests besides financial interests. Please respond.

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, and such should be noted in the IRB meeting minutes.

Please submit to OHRP your response to the above findings, questions, and concerns no later than July 31, 2001.

OHRP appreciates your institution's continued commitment to the protection of human research subjects. Do not hesitate to contact me if you have any questions regarding this matter.

Sincerely,

Kristina C. Borror, Ph.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Mrs. Elizabeth Crigler, Executive Officer, IRB, GU
Dr. Willard A. Barnes, Chair, IRB, GU
Dr. Kevin Schulman, GU
Commissioner, FDA
Dr. David Lepay, FDA
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