DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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October 4, 2000

Kenneth L. Dretchen, Ph.D.
Dean of Research and Graduate Education
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), formerly the Office for Protection from Research Risks (OPRR), has reviewed your report of April 20, 1999, regarding the above referenced research project. OHRP apologizes for the delay in responding to your report.

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) Department of Health and Human Services (HHS) regulations at 45 CFR 46.101(b) delineate six specific categories of exempt activities. OHRP finds that the institution inappropriately applied exempt status to earlier versions of this project under the exempt category stipulated by HHS regulations at 45 CFR 46.101(b)(2) (i.e, research involving the use of educational tests, survey procedures, interview procedures or observations of public behavior) in November 1992 and September 1993.

In particular, OHRP notes that the proposed research was not exempt because it involved

subject deception and manipulation of subjects' environment in order to measure a behavioral response, and thus did not solely involve use of educational tests, survey procedures, interview procedures or observations of public behavior. OHRP acknowledges that the project did undergo an expedited review procedure by the IRB in April 1994 prior to funding by HHS and enrollment of subjects.

(2) HHS regulations at 45 CFR 46.116 stipulate that no investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative, except where the Institutional Review Board (IRB) has waived the requirement to obtain informed consent under the provisions of HHS regulation at 45 CFR 46.116(d).

(a) OHRP finds that the investigators did not obtain the legally effective informed consent of the subjects who participated in this research.

(b) OHRP finds no evidence that the IRB made and documented the four specific findings required by HHS regulations at 45 CFR 46.116(d)(1)-(4) for waiver of informed consent when it approved this research.

OHRP emphasizes that when reviewing and approving a research project under an expedited review procedure, the IRB Chair, or an experienced IRB member designated by the Chair, must still fulfill all of the responsibilities and requirements of the HHS regulations at 45 CFR Part 46.

Recommended Action: Where 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. For protocols undergoing expedited review, these findings should be documented in the IRB record by the IRB Chair, or an experienced IRB member designated by the Chair.

OHRP has the following additional questions and concerns regarding this research:

(3) 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 reviewing the IRB records provided with your report, it appears that the IRB did not receive and review a copy of HHS-funded grant application that was signed and dated by

the principal investigator on February 18, 1994. Instead, it appears that on March 16, 1994, the principal investigator submitted only a portion of the grant application that he signed and dated on June 23, 1993.
Please respond. In your response, clarify whether the IRB receives and reviews copies of complete grant applications proposing human subject research that are submitted for Federal support, and if so, indicate how long the IRB has been following such a policy.

(4) HHS regulations at 45 CFR 46.111(a)(1) and (2) require that, in order to approve research, the IRB shall determine that risks to subjects are minimized and reasonable in relation to anticipated benefits, if any, to the subjects and the importance of the knowledge that may reasonably be expected to result.

OHRP is concerned that the IRB failed to adequately consider the reasonably foreseeable risks to subjects enrolled in this research. For example, given the nature of the subject population (i.e., physicians) and the high likelihood that many of these subjects would read about this research in professional medical journals, there appears to have been a reasonably foreseeable risk of possible emotional or psychological harm to the subjects when they learn that they had participated in deceptive research and may have demonstrated racial or gender bias in their responses to the researchers. There appears to be no evidence that the IRB Chair considered such risks when he reviewed and approved this research under an expedited review procedure. Please respond.

(5) HHS regulations at 45 CFR 46.109(a) require that the IRB review and approve all non-exempt human subject research. OHRP is 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*.

In reviewing the IRB records related to IRB protocol number 113-94, OHRP is unable to identify any IRB-approved protocol that included (i) randomization of medical students to different experimental groups; and (ii) deception of such subjects. OHRP notes that the principal investigator submitted to the IRB a memorandum dated April 26, 1996,

requesting approval to distribute a flyer and e-mail advertisement for protocol number 113-94 to medical students at Georgetown University (GU). It appears that the IRB Chair approved the principal investigator's request on April 29, 1996 without seeking additional information from the investigator. 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.

(6) 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 notes that the grant application signed and dated by the principal investigator on February 18, 1994 stated that subjects would be paid $25 for participating in the research, whereas the Special Article in *The New England Journal of Medicine* regarding this research reported that physician subjects were offered a food gift. It appears that the IRB did not review and approve this change in the remuneration of the subjects. Please respond.

(7) OHRP is concerned 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, it appears that the recruitment postcard sent to prospective physician subjects was not reviewed and approved by the IRB. Please respond.

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

(8) HHS regulations at 45 CFR 46.115(a)(2) require that minutes of IRB meetings be in sufficient detail to show the vote on IRB actions including the number of members voting for, against, and abstaining; the basis for requiring changes in or disapproving research; and a written summary of the discussion of controverted issues and their resolution. Based upon its review of the IRB minutes provided with your report, OHRP finds that through at least April 17, 1997, the minutes of IRB meetings uniformly failed to meet these requirements.

Furthermore, the minutes of IRB meetings appear to indicate that little substantive review takes place at convened meetings. In particular, OHRP is concerned that the minutes of IRB meetings appear to reveal scant evidence that IRB approval of research is consistently based on consideration of the determinations required under HHS regulations at 45 CFR 46.111. For example, the IRB appears not to consider systematically and

rigorously such issues as equitable selection of subjects and subject recruitment, privacy and confidentiality protections, and special protections required for vulnerable subjects. Please respond.

(9) OHRP is concerned 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(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.

Written IRB policies and procedures should provide the operational details for each of the above referenced IRB procedures. In order to assist GU in the evaluation and revision of its written IRB policies and procedures, please see the enclosed Guidance for Formulating Written IRB Policies and Procedures.

(11) 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 that do not harm the individual's relationship with the University or its employees, this language may not satisfy the requirements of HHS regulations at 45 CFR 46.116(a)(8). Please respond.

Please submit to OHRP your response to the above findings, questions, and concerns no later than November 10, 2000.

Please provide the following with your response:

(1) Any revised written IRB policies and procedures.

(2) IRB minutes for the past 4 months.

(3) A description of GU's program for ensuring that all IRB members, all IRB staff, and all research investigators are appropriately educated, on an ongoing basis, about the regulatory requirements for the protection of human subjects.

(4) A description of any corrective actions that have been or will be implemented at GU in response to any instances of noncompliance with HHS regulations for the protection of human subjects that you identify during your investigation of these matters.

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

Enclosure: Guidance for Formulating Written IRB Policies and Procedures

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
Dr. James F. McCormack, FDA

Dr. Greg Koski, OHRP
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. J. Thomas Puglisi, OHRP
Dr. Katherine Duncan, OHRP
Mr. George Gasparis, OHRP
Dr. Jeffrey M. Cohen, OHRP