DEPARTMENT OF HEALTH & HUMAN SERVICES

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August 15, 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: Functional MRI Studies of the Pathophysiology of Dyslexia
IRB Project Number: 250-96
Principal Investigator: Guinevere Frauke Eden, Ph.D.

Dear Dr. Dretchen:

The Office for Human Research Protections (OHRP) has reviewed your report of October 31, 2000, regarding the above referenced research project conducted by Georgetown University (GU).

Based upon its review of the documents provided with your report, OHRP makes the following determinations:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.110(b)(2) permit use of expedited procedures for review of minor changes to previously approved research. OHRP finds that the GU Institutional Review Board (IRB) has employed expedited procedures to review changes that exceed this limitation. For example, the following major changes to the protocol were reviewed and approved in an expedited procedure:

(a) March 19, 1997– inclusion of children in behavioral studies, among other changes.

(b) January 7, 1998 – inclusion of children in the MRI studies.

(c) November 24, 1999 – inclusion of subjects with ADHD who would be withdrawn from ritalin.

(d) November 24, 1999 – inclusion of deaf individuals with dyslexia.

Action 1– Required: Please provide OHRP with a corrective action plan to ensure that only minor changes to protocols are reviewed in an expedited manner.

(2) OHRP finds that the procedures for enrolling subjects failed to minimize the possibility of coercion or undue influence as required by HHS regulations at 45 CFR 46.116. The Principal Investigator enrolled a minor subject who was staying in her house and who was the daughter of her fiancee, and another minor subject who was under her employ.

Action 2– Required: Please provide OHRP with a corrective action plan to ensure that no investigators at GU enroll such subjects, minor or otherwise, who could be coerced or unduly influenced to participate. OHRP notes that the Principal Investigator has been advised "not to enroll any individuals where there are familial relationships or supervisory relationships." OHRP suggests that such a policy be adopted University-wide.

(3) HHS regulations at 45 CFR 46.117(a) require that informed consent be documented by the use of a written consent form approved by the IRB. OHRP finds that the Principal Investigator used an informed consent document for the complainant's daughter that was not approved by the IRB.

Action 3– Required: Please provide OHRP with a corrective action plan to ensure that all informed consent documents used in research at GU are reviewed and approved by the IRB.

(4) On August 21, 1998, the IRB suspended the above-referenced protocol in response to a phone call from the complainant. OHRP finds that this suspension was not reported to OHRP, as required by HHS regulations at 45 CFR 46.103(b)(5).

Action 4– Required: Please provide OHRP with a corrective action plan to ensure that all suspensions or terminations of IRB approval are promptly reported to OHRP.

(5) 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 following protocol changes were implemented without IRB approval:

(a) The protocol called for pregnancy tests for all women/girls of child-bearing age. The Principal Investigator was not adhering to that practice.

(b) The Principal Investigator did not follow the protocol regarding having parents in the room during the MRI and conducting "feel good" sessions to get children used to the MRI.

(c) Several times the Principal Investigator used non-approved versions of the advertisements.

Corrective Action: OHRP acknowledges that GU had previously indicated that the GU IRB is revising its protocol review and continuing review forms to request such information. OHRP also acknowledges GU's assertion that "[t]he PI now follows those procedures strictly." OHRP finds that this corrective action adequately addresses the finding and is appropriate with GU's Multiple Project Assurance.

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

(6) GU offered to report to OHRP by March 1, 2001, a summary of the findings of the risk assessment. OHRP has never received this summary. Please provide OHRP a copy of these findings.

(7) On August 27, 1998 the IRB subcommittee set up to investigate this matter made several findings and recommendations. The recommendations included resuming the protocol with adult subjects only, requiring the chair of the Department of Pediatrics to sign off on all protocols involving children, a periodic review of this protocol's participant records, giving all girls of child-bearing age pregnancy tests, encouraging appropriate medical consultation for subjects with significant medical conditions, and continuing review for this project after every 5 subjects enrolled. OHRP has the following concerns and questions regarding the implementation of these recommendations:

(a) The Principal Investigator resumed the protocol with children, under a different protocol name and number. It is not clear if the new protocol was ever reviewed by the full IRB. The protocol was not submitted initially, only the informed consent document. When the protocol was submitted, it was the old protocol, with inclusion of adults and children.

(b) Was continuing review conducted after every 5 subjects were enrolled?

(c) The Principal Investigator only required girls to have pregnancy tests prior to enrollment. It is not clear why women were not also required to have pregnancy tests, as women may be unaware of pregnancies as are girls.

(d) Did the Principal Investigator obtain Department of Pediatrics review for the new protocol involving children?

Please respond.

(8) A September 22, 1998 memo from the PI to the IRB requested a change in compensation to vary with the days of the week and had a single informed consent document with check boxes for the different procedures and compensation amounts. OHRP is concerned that the informed consent document was very confusing. Please respond.

OHRP provides the following guidance:

(9) 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.

Please submit to OHRP your response to the above determinations, questions and concerns no later than September 28, 2001. If upon further review of the concerns and questions, UC identifies additional instances of non-compliance with the HHS regulations for protection of human subjects, please include detailed corrective action plans to address the noncompliance.

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. Guinevere F. Eden, GU

Commissioner, FDA
Dr. David Lepay, FDA
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