DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 24, 2002

John H. Lichten
Dean for Administration and Finance
Harvard School of Public Health
677 Huntington Avenue
Boston, MA 02115

RE: Human Research Subject Protections Under Multiple Project Assurance (MPA) M-1208 and Federalwide Assurance -FWA 2642

Dear Mr. Lichten:

The Office for Human Research Protections (OHRP), has reviewed your report of May 9, 2002 regarding human subject research conducted at the Harvard School of Public Health (HSPH). These reports contained information about the following research projects:

Research Project: Petrochemical Exposure and Reproductive Outcomes
Principal Investigator: Dr. David C. Christiani
HHS Project Number: R01 OH 03027
HSPH Project Number: 9203PETR

Research Project: Lead, Endocrine Disruption and Reproductive Outcomes
Principal Investigator: Dr. Xiping Xu
HHS Project Number: R01 ES08337
HSPH Project Number: 9602LEAD

Research Project: Rotating Shift Work and Reproductive Outcomes
Principal Investigator: Dr. Dr. Xiping Xu
HHS Project Number: R01 HD32505
HSPH Project Number: 9401ROTA

Research Project: Molecular Epidemiology of Preterm Birth: Environmental and

Genetic Interactions
Principal Investigator: Dr. Dr. Xiping Xu
HSPS Project Number: 9804MOLE

Research Project: Molecular Genetic Epidemiologic Study on Obesity in China
Principal Investigator: Dr. Dr. Xiping Xu
HSPH Project Number: 9611MOLE

Research Project: Genetics of Hypertension and its Intermediate Phenotypes
Principal Investigator: Dr. Xiping Xu
HSPS Project Number: 9902GENE
HHS Project Number: R01 HL64109

Research Project: Longitudinal Investigation of Respiratory Disease in Chinese Textile Workers
Principal Investigator: Dr. David C. Christiani
HHS Project Number: OH02421
HSPH Project Number: 8701LUNG

Research Project: Genetic susceptibility to the effects of aromatic solvents on reproductive health
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9707GENE

Research Project: Biomarkers for Human Reproductive Epidemiology
Principal Investigator: Dr. Xiping Xu
HHS Project Number: P01 ES06198
HSPH Project Number: 9810BIOM

Research Project: Genetic Epidemiology of Complex Traits Using Twins
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9711GENE

Research Project: The Genetics of Airway Responsiveness and Lung Function
Principal Investigator: Dr. Xiping Xu
HHS Project Number: 1R01 HL56371
HSPH Project Number: 9912GENE

Research Project: The Genetics of Nicotine Addiction Vulnerability
Principal Investigator: Dr. Xiping Xu
HHS Project Number: 1R01 DA12905
HSPH Project Number: 9902GEN1

Research Project: Organophosphate Pesticide Exposure and Reproductive Toxicity
Principal Investigator: Dr. Xiping Xu
HSPH Project Number: 9605ORGA

In its March 28, 2002 letter, OHRP required that HSPH develop satisfactory corrective action plans to address the following determinations made by OHRP regarding the above-mentioned research projects and HSPH's system for protecting human subjects:

(1) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(b)(4)(iii) require that the institutional review board (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 found that protocol changes were implemented without IRB approval.

HHS regulations at 45 CFR 46.103(b)(4) require that the IRB have written policies and procedures for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review. OHRP suggested that, given the breadth and seriousness of Dr. Xu's violations, HSPH consider implementing a plan to monitor his research records on an ongoing basis to verify that he is conducting the research in accordance with the IRB-approved protocols.

Corrective Action: OHRP acknowledges that HSPH has made much progress in implementing its Quality Improvement Plan including revising the Operations Manual; the development of new and improved forms, worksheets, and letters to investigators; improvements in the online tutorial; new education coordinator and tracking system; new training requirements and workshop; improved primary reviewer system, follow-up and reminders to investigators; new and improved space for the IRB, improved minutes of IRB meetings, and monitoring of the consent process by the HSPH IRB.

Furthermore, OHRP acknowledges that HSPH and its IRB have suspended all of the above-referenced research projects that were still enrolling subjects and has imposed a hold on new research applications on which Dr. Xu is the principal investigator. HSPH also has implemented a plan to monitor Dr. Xu's ongoing research involving human subjects, involving oversight of data management systems by an appointed data monitor, and has plans to conduct consent monitoring at international sites. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH FWA. OHRP suggests that when the HSPH and its IRB permit Dr. Xu to resume research that involves interactions or interventions with human subjects, HSPH should consider implementing a plan to monitor his research on an ongoing basis to verify that he is conducting the research in accord with the IRB-approved protocols.

(2) OHRP found that when reviewing these protocol applications, the HSPH IRB often lacked sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

Corrective Action: OHRP acknowledges that the HSPH IRB has hired a Data Coordinator to review the responsive materials submitted by investigators after requests from the IRB. In addition, the IRB is working to improve its database to enable IRB staff to manage protocol data, including contingent approvals and deferrals that require responsive material from investigators, and has applied for NIH funding for a new University-wide database. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH FWA.

(3) HHS regulations at 45 CFR 46.103(b) and 46.109(a) require that research involving human subjects be reviewed and approved by an IRB. HHS regulations at 46.111(a)(4) require that the IRB determine that informed consent will be sought from each prospective subject in accordance with, and to the extent required by, HHS regulations at 45 CFR 46.116. OHRP found that the Dr. Xu conducted several research studies without IRB review and approval, and possibly without informed consent of the subjects.

Corrective Action: OHRP acknowledges that the HSPH IRB has investigated the research projects that were not reviewed and approved by the HSPH IRB. HSPH indicated that written informed consent of the subjects was obtained in all of these studies. The HSPH IRB determined that these activities may have been exempt from the human subject protection regulations in that Dr. Xu only received previously collected, de-identified samples and that recontact of subjects was not indicated. OHRP also acknowledges that one of the questionnaires noted by OHRP in its March 28, 2002 letter that was not reviewed by the IRB was for the field team to manage data, and was not to be administered to human subjects, and that the other questionnaire mentioned by OHRP has been reviewed and approved by the HSPH IRB. OHRP finds that these responses and corrective actions adequately address the above finding and are appropriate under the HSPH FWA.

(4) HHS regulations at 45 CFR 46.111(a) state that in order to approve research, the IRB shall determine that the following requirements, among others, are satisfied: (a) risks to subjects are minimized; and (b) risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that reasonably may be expected to result; and (c) selection of subjects is equitable.

OHRP found that, when reviewing protocol # R01 HL64109, the HSPH IRB failed to adequately consider whether or not (a) the subjects would benefit from this research, either in the short term or the long term; (b) the risks to which they are subjected might outweigh the benefits that may result from the research; and (c) that the subject selection was equitable.

Corrective Action: OHRP acknowledges that the HSPH again reviewed this study, having

received more information about the risks and benefits involved, and found benefits to subjects and equitable selection of subjects. OHRP acknowledges that, from now on, the HSPH IRB will require data at continuing review from investigators conducting research involving vulnerable populations indicating the number of subjects referred to treatment or receiving other forms of affordable advantages as a result of study participation. The IRB also will verify this type of information in site visits to a selection of studies. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH FWA. OHRP again emphasizes that research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.

(5) HHS regulations at 45 CFR 46.117(a) require that, unless appropriately waived by the IRB, informed consent shall be documented by the use of a written consent form approved by the IRB and signed by the subject, or the subject's legally authorized representative. OHRP found that consent was not documented in writing for the Chinese textile workers (only oral consent) for project # OH02421 and for project # R01 HL64109, and that the HSPH IRB failed to find and document that oral consent was appropriate under the regulations.

Corrective Action: OHRP acknowledges that the IRB has reminded Drs. Xu and Christiani that when oral consent is used, there shall be a witness to the oral presentation and the IRB shall approve a written summary of what is to be said to the subject. In addition, the IRB has increased education on the process of oral consent at training workshops, in letters, and in other forms of communications with investigators. OHRP also acknowledges that the HSPH IRB has improved its procedures for finding and documenting that a waiver of signed consent document is appropriate under the regulations, to comply with 45 CFR 46.117. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH FWA.

(6) HHS regulations at 45 CFR 46.110(b)(2) permit use of expedited review procedures for the initial or continuing review of certain minimal risk research and for reveiw of minor changes to previously approved research. OHRP found that the HSPH IRB employed expedited procedures for the initial review of research and changes that exceed these limitations on expedited review. In addition, OHRP found that HSPH IRB members were not advised of (a) expedited initial or continuing review approvals of research protocols, or (b) expedited approvals of minor changes in research protocols, as required by HHS regulations at 45 CFR 46.110(c).

Corrective Action: OHRP acknowledges that the HSPH IRB now includes a report of expedited actions as an appendix to the minutes stating the regulatory category justifying expedited review, which is reviewed by the IRB members; any concerns regarding the expedited review are discussed in a convened meeting. In addition, the HSPH IRB has developed new review forms for continuing review and amendments to ensure appropriate decisions regarding expedited review. OHRP finds that these corrective actions adequately

address the above findings and are appropriate under the HSPH FWA.

(7) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the IRB at intervals appropriate to the degree of risk and not less than once per year. OHRP found that the principal investigator continued to conduct research on project # 1R01 DA12905 even though the protocol had not received continuing review and approval at least once per year.

Corrective Action: OHRP acknowledges that the HSPH IRB has devised joint procedures with the Office for Financial Services to help ensure that other investigators do not conduct research past the date of approval. In addition, the HSPH IRB's consent and records monitoring program will allow the IRB to identify lapses and unapproved activity and to follow up with the Office for Financial Services, and the new database will electronically alert investigators and the IRB of lapses. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH FWA.

(8) HHS regulations at 45 CFR 46.116(d) require that the IRB find and document four specific criteria when approving waiver or alteration of some or all of the required elements of informed consent. OHRP expressed concern that the HSPH IRB may not have satisfied these requirements when reviewing by expedited review certain projects that propose waiver of informed consent (see, for example, protocol # 0106PATH, reported to the HSPH IRB 6/15/01).

Corrective Action: OHRP acknowledges HSPH's statement that the IRB has begun to make the required findings, using new waiver checklists as guides. In addition, the minutes have been reformatted to document the findings for research reviewed at convened meetings. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the HSPH FWA.

(9) In its March 28, 2002 letter to HSPH, OHRP expressed concern that several subjects in the projects "Genetics of Hypertension and its Intermediate Phenotypes" and "Molecular Genetic Epidemiologic Study on Asthma" may have been enrolled and undergone study interventions prior to signing informed consent documents and that subjects did not date the informed consent documents themselves, or that the documents may have been back-dated.

OHRP acknowledges HSPH's statements that the date listed was actually the subject's arrival date, not the enrollment date, and that no subjects underwent study interventions prior to signing the informed consent document. OHRP also acknowledges HSPH's statement that for these studies the researchers dated the informed consent documents at the time of obtaining consent to ensure that the dates were all written by the Western calendar rather than the Chinese lunar year.

(10) In its March 28, 2002 letter to HSPH, OHRP expressed concern that statements in several journal articles are in conflict with the recruiting practices outlined in all of Drs. Xu and

Christiani's research protocols– that couples were recruited after obtaining permission to conceive a child. The articles indicated that couples were recruited at the time of marriage registration.

OHRP acknowledges HSPH's statements that none of the subjects in these two studies had obtained a formal marriage license or conception certificate before being invited to participate, but had obtained oral permission to marry and conceive, pending paperwork completion and a pre-marital examination.

OHRP remains concerned that approaching women before they had obtained final, official permission to marry or conceive may have failed to minimize the possibility of coercion because prospective subjects may have thought that it might improve their chances for marriage or conception permission. OHRP also is concerned that only 2% of subjects approached in the rural province of Anqing refused to participate, which may indicate reluctance to refuse. OHRP expects that for any similar research reviewed by the HSPH IRB in the future, the IRB will ensure that provisions are included in the research to minimize the possibility of coercion or undue influence.

(11) In its March 28, 2002 letter to HSPH, OHRP expressed concern about Chinese news reports of a farmer in Toutuo, Anhui Province who was a participant in the HSPH genetic research study on asthma. The farmer told the reporter that he had blood taken from him on 2 separate occasions, November 1996 and March 1997, but neither was asked to sign nor was given an informed consent document. He stated that the researchers came later and asked him to sign a paper; he was not told what the paper said, and he could not read it without his glasses. The date on this informed consent document is apparently October of 1997. The farmer told the reporter that he did not know he was participating in the genetic study on asthma; he said he was willing to give blood so that he could get some treatment for his children's asthma.

OHRP acknowledges that HSPH cannot confirm nor deny that this subject was enrolled in the Millenium study, but he was apparently not enrolled in protocol # HL56371.

OHRP has the following unresolved concerns and questions:

(12) [redacted]

[redacted]

(13) [redacted]

(14) [redacted]

(15) [redacted]

(16) [redacted]

[redacted]

(17) [redacted]

(18) [redacted]

Please submit to OHRP your response to questions and concerns in items (12)-(18) no later than August 30, 2002. If upon further review of this matter you identify additional instances of non-compliance with the HHS regulations for protection of human subjects, please describe the corrective actions that have been or will be taken to address the noncompliance.

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

cc: Ms. Sarah Putney, HSPH
Dr. Troyen A. Brennan, Chair, IRB, HSPH
Dr. David Christiani, HSPH
Dr. Xiping Xu, HSPH
Commissioner, FDA
Dr. David Lepay, FDA
Dr. Melody H. Lin, OHRP
Dr. Michael A. Carome, OHRP
Dr. Jeffrey Cohen, OHRP
Mr. George Gasparis, OHRP
Ms. Yvonne Higgins, OHRP

Mr. Barry Bowman, OHRP