DEPARTMENT OF HEALTH & HUMAN SERVICES

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Office of Public Health and Science

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March 28, 2002

Keith A. Marcotte
Vice President for Research Administration
Brigham and Women's Hospital
75 Francis St.- 10BPW
Boston, MA 02115

RE: Human Research Subject Protections Under Federal Wide Assurance FWA- 484

Research Project: Molecular Genetic Epidemiologic Study on Asthma
Principal Investigator: Dr. Xiping Xu
B&WH Project Number: 94-06932

Research Project: Genetics of Airway responsiveness and lung function
Principal Investigator: Dr. Xiping Xu
HHS Project Number: R01 HL56371-02
B&WH Project Number: 96-08190

Dear Mr. Marcotte:

The Office for Human Research Protections (OHRP) has reviewed your report of January 30, 2002 regarding the above-referenced research conducted by the Brigham and Women's Hospital (B&WH).

Based upon its review, OHRP makes the following determinations:

A. OHRP Findings Regarding Project Number R01 HL56371-02

(1) In accordance with HHS regulations at 45 CFR 46.103(b) and 46.109(a), the IRB must review and approve all non-exempt human subject research covered by an assurance. OHRP finds that certain human subject research was conducted by Dr. Xu without IRB review.

B&WH acknowledged that Dr. Xu collected data for a "Pilot Study" for which study enrollment began in February, 1995, seven months prior to B&WH IRB approval. In addition, Dr. Xu collaborated with Chinese investigators in a feasibility study in 1994 without approval of the B&WH IRB.

Corrective Action: OHRP acknowledges that the investigators have been informed that inconsistencies and incorrect reporting of enrollment has made it difficult for OHRP and B&WH to verify accuracy of enrollment numbers. The investigators have been instructed to review all publications and submit formal corrections as appropriate. OHRP finds that these corrective actions are appropriate under the B&WH FWA.

Action 1– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action plan to assure that all investigators at B&WH seek IRB review and approval for all non-exempt human subject research prior to conducting that research.

(2) Department of Health and Human Services (HHS) regulations at 45 CFR 46.111(a)(1), (2), and (3) require respectively that, in order to approve research, the IRB shall determine that: risks to subjects are minimized; risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects and the importance of the knowledge that may reasonably result; and selection of subjects is equitable. OHRP notes the following:

> (a) The HL56371 grant application noted that medication use for asthma is rare in China. The protocol involved several procedures involving risks to subjects with little prospect of benefit in the short term, since asthma diagnosed by the researchers was unlikely to be treated when the research was reviewed and approved, as the Chinese were not widely treating asthma at the time. Although the principal investigator has noted that affordable drugs for the treatment of asthma were introduced to these regions by the collaborators on this research, the B&WH IRB did not know that this was going to happen at the time they reviewed the research and did not consider that selection of subjects may not have been equitable. In addition, the drugs that have been introduced to these rural areas are not Western made drugs, such as would be developed by this research, but China-made drugs, arguing that the rural population is unlikely to benefit from this research in the long-term. As the Belmont Report notes:
>
> > ...it can be seen how conceptions of justice are relevant to research involving human subjects. For example, the selection of research subjects needs to be scrutinized in order to determine whether some classes (e.g., welfare patients, particular racial and ethnic minorities, or persons confined to institutions) are being systematically selected simply because of their easy availability, their compromised position, or their manipulability, rather than for reasons directly related to the problem being studied. Finally, whenever research supported by public funds leads to the development of therapeutic devices and procedures,

> justice demands both that these not provide advantages only to those who can afford them and that **such research should not unduly involve persons from groups unlikely to be among the beneficiaries of subsequent applications of the research.** (Emphasis added)

(b) The protocol "Genetics of Airway Responsiveness and Lung Function" required a family size of 4 or greater. This requirement does not appear to be consistent with the "one child family" rule of China. Although in their January 30, 2002 letter B&WH noted that the principal investigator indicated that the rule was relaxed in rural areas, the article by Susan Greenhalgh (Population & Development Review, 1986, 12(3): 491-515) provided by B&WH makes it clear that although the rules were relaxed for second children under very specific circumstances, "third children were not supposed to be allowed under any circumstances." OHRP is concerned that identification of families having 3 or more children participating in the research study could have placed them at risk in regard to this rule and that the IRB did not adequately consider this risk. B&WH stated that the average family size for protocol #94-06932 was 4.5, indicating that many families had at least 3 children.

Based upon the above observations, OHRP finds that the 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; and (c) that the subject selection was equitable.

Action 2– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action plan to address this finding.

(3) OHRP finds that the informed consent documents reviewed and approved by the B&WH IRB for these studies failed to adequately address the following element required by HHS regulations at 45 CFR 46.116(a):

> Section 46.116(a)(8): A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. The informed consent document approved by the B&WH IRB on September 29, 1995 stated that withdrawal or discontinuation of study "will not affect regular treatments or medical care in any way," but the informed consent document failed to include a statement that participation in the study was voluntary, and that nonparticipation will involve no penalty or loss of benefits to which the subject is otherwise entitled. In addition, the standard language for B&WH informed consent documents stated "Participation in this study is voluntary....Your present or future care will not be affected should you choose not to participate. If you decide to participate, you can change your mind and drop out of the study at any time

without affecting your present care in the Hospitals." There could be penalties or loss of benefits unrelated to "present or future care....in the Hospitals."

Action 3– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action plan to address this finding.

(4) HHS regulations at 45 CFR 46.404-407 require specific findings by the IRB for approval of research involving children. OHRP's review of IRB documents revealed no evidence that the B&WH IRB made the required findings when reviewing this research involving children ("Molecular Genetic Epidemiologic Study on Asthma"--6 years and older; "Genetics of Airway Responsiveness and Lung Function"--8 years and older.) Although B&WH's January 30, 2002 response to OHRP stated that "[t]he importance of assent and sensitivity to the child study participant was part of standard review" this does not address all the required findings under HHS regulations at 45 CFR 46.404-407.

Corrective Actions: OHRP acknowledges that current B&WH IRB policies and procedures focus much more attention on the issue of child assent. However, OHRP again notes that assent is not the only issue that must be addressed in accordance with HHS regulations at 45 CFR 46.404-407.

Action 4– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action to ensure that the IRBs make the specific findings required by HHS regulations at 45 CFR 46.404-407 when approving research involving children.

(5) OHRP finds that when reviewing this protocol application, the IRB appeared to lack sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111. In particular, OHRP notes the following:

(a) On June 18, 1998 the principal investigator reported 5,556 recruited subjects, however 16,686 subjects had been recruited.

(b) In an article from this research in the *American Journal of Respiratory and Critical Care Medicine*, it was stated that letters were sent to each eligible family explaining the study. OHRP finds that this letter was never reviewed and approved by the IRB.

Action 5: Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action plan to ensure that the B&WH IRBs receive and review sufficient information to make the determinations required for approval of research under HHS regulations at 45 CFR 46.111.

(6) 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 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. 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 at URL http://ohrp.osophs.dhhs.gov/humansubjects/guidance/hsdc95-01.htm). Furthermore, the minutes of IRB meetings should document separate deliberations, actions, and votes for each protocol undergoing continuing review by the convened IRB. OHRP finds that continuing review by the B&WH IRB for this project was not substantive and meaningful.

Corrective Action: OHRP acknowledges that a different continuing review system has been in place at B&WH since June of 1999. Two additional IRBs were formed to conduct continuing review in accordance with HHS regulations and OHRP guidance. In addition, B&WH contracted in August 1999 to have an independent audit of the IRBs, resulting in further clarifications and modifications. The B&WH IRBs now also require that information regarding off-site enrollment of subjects and complete, detailed progress reports for continuing review of research. OHRP finds that these corrective actions adequately address the above finding and are appropriate under the B&WH MPA.

(7) 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 may have been implemented without B&WH IRB approval:

(a) The principal investigator changed the recruitment strategy to have the local physicians divide potential study families into three categories and that the local physicians accompanied those families that were most likely to meet study criteria to the study center.

(b) The "Molecular Genetic Epidemiologic Study on Asthma" was only approved for enrollment of 2,000 subjects. The principal investigator enrolled 16,686 subjects.

(c) The investigators changed the compensation of subjects from $10 to providing them meals and transportation plus cash for time off of work without getting B&WH IRB approval. This change was also made to the Chinese informed consent document without IRB approval.

(d) Subjects were recruited from 8 counties around Anqing City, although the B&WH IRB approved recruitment from only two counties.

(e) Numerous changes were made to the Chinese informed consent document, apparently without B&WH IRB review and approval, including changing the volume of the blood sample from two teaspoons to six teaspoons, and changing the risk of the bronchodilator from tachycardia to bradycardia.

Corrective Actions: OHRP acknowledges that the requirements for prior approval of all changes to the protocol and the consent form have been reviewed with the investigator and that, in the future, all changes will be submitted for review and approval prior to implementation. OHRP finds that these corrective actions are appropriate under the B&WH FWA.

Action 6– Required: By May 10, 2002, please provide OHRP with a satisfactory corrective action plan to ensure that no B&WH investigator implements changes to protocols without prior IRB review and approval.

Furthermore, HHS regulations at 45 CFR 46.103(a) and 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. Given the breadth and seriousness of Dr. Xu's violations, please indicate if B&WH has considered implementing a plan to monitor any current research records on an ongoing basis to verify that he is conducting the research in accord with the IRB-approved protocols.

(8) Department of Health and Human Services (HHS) regulations at 45 CFR 46.103(a) require that each institution "engaged" in human subjects research provide OHRP with a satisfactory Assurance to comply with the regulations, unless the research is exempt under 45 CFR 46.101(b). (Please see OHRP guidance on engagement in research at URL http://ohrp.osophs.dhhs.gov/humansubjects/assurance/engage.htm)

OHRP finds no evidence that a Single Project Assurance was obtained for the site of this research in China, the Anqing Meizhong Biomedical Environmental Health Research Institute.

Corrective Action: OHRP acknowledges that the current policy of the B&WH IRBs require that a determination be made whether an SPA must be obtained for any federally funded studies which involve active research participation of co-investigators at non-MPA sites. OHRP finds that this corrective action adequately addresses the finding and is appropriate under the B&WH MPA.

(9) HHS regulations at 45 CFR 46.107(a) require that the IRB membership be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. OHRP finds that the B&WH IRB lacked the background and

expertise to review the above-referenced research because of its apparent failure to consider of the cultural conditions, including the social, economic, and political status, of the subject population.

Corrective Action: OHRP acknowledges that the B&WH IRBs are increasingly sensitive to ethical issues related to conducting research in developing countries and has sought additional consultation from other individuals, such as a researcher or a physician not involved with the study who is from and/or knowledgeable about the country in question. OHRP finds that this corrective action adequately addresses the finding and is appropriate under the B&WH MPA.

B. OHRP Concerns and Questions Regarding Project Number R01 HL56371-02

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

(10) The January 10, 2002 China Daily contains an article by Xiong Lei that tells the story of a farmer in Toutuo, Anhui Province who was a participant in the 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 was not asked to sign nor 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. Was this subject enrolled in protocol #1R01 HL56371? Does B&WH have knowledge of other allegations of post-dated or post-signed informed consent documents for this or other studies? Please respond.

(11) B&WH provided OHRP with a copy of each informed consent document (with subject's names redacted.) After review of these documents, OHRP is concerned that the handwriting for the dates next to the subject's signatures appear to be identical. Furthermore, OHRP is concerned that subjects did not date the informed consent documents themselves, even those subjects who could write (as evidenced by their signature), or that the documents may have been back-dated. Please respond.

C. OHRP Findings Regarding General Human Subjects Protections at B&WH

(12) OHRP finds that B&WH did not have adequate written IRB policies and procedures that describe the following activities, as required by HHS regulations at 45 CFR 46.103(b)(4) and (5)(a):

(i) The procedures which the IRB will follow for determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(ii) The procedures which the IRB will follow for determining 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.

Corrective Action: OHRP acknowledges that the B&WH IRBs have revised their policies and procedures to address some of these findings. By May 10, 2002, please provide OHRP with a copy of these revised policies and procedures.

Please submit to OHRP your response to the above determination, questions and concerns no later than May 10, 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. **Please note OHRP's new address.**

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: Dr. Joseph H. Antin, Chair, IRB #1, B&WH
Dr. Julian L. Seifter, Chair, IRB #2, B&WH
Dr. Jeffrey Otten, President, B&WH
Dr. P. Pearl O'Rourke, B&WH
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Dr. Xiping Xu, B&WH
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Ms. Yvonne Higgins, OHRP
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