DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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July 24, 2007

Kathleen Matt, Ph.D.
Assistant Vice President for Research
Arizona State University
Foundation Building, Ste 245, PO Box 877105
Tempe, AZ 85287-7105

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 9102

Research Project: Mechanisms of Protections in HIV – Exposed Seronegative Partners of HIV Seropositive Patients
Principal Investigator: Charles Arntzen
Project Number: HS # 0407001903 and HS # 0509000193

Research Project: Early Language and Literacy Interventions
Principal Investigator: Jeanne Wilcox
Project Number: HS # 0309001372 and HS # 0512000492

Research Project: Molecular Regulation of Muscle Glucose Metabolism in Man
Principal Investigator: Lawrence Mandarino
Project Number: HS #0501002211

Research Project: Gila River Diabetes Reduction Initiative
Principal Investigator: Pamela Kulinna
Project Number: HS # 0509000171

Research Project: Salt River Pima-Maricopa Indian Community Physical Activity and Health Education Initiative
Principal Investigator: Pamela Kulinna
Project Number: HS # 0408001947

Research Project: Coordination of Control of Muscle Activity for Grasping Movements
Principal Investigator: Marco Santello
Project Number: HS #0601000564

Research Project: Analysis of Blood Samples

Principal Investigator: Bert Jacobs
Project Number: HS # 0506000016

Research Project: Olivenol Study in Individuals with Arthritis
Principal Investigator: Kathleen Matt
Project Number: HS # 0308001356

Research Project: Use of Composite Images in Eyewitness Identification
Principal Investigator: Dawn McQuiston-Surrett
Project Number: HS # 0309001408 and # 0507000070

Dear Dr. Matt:

The Office for Human Research Protections (OHRP) has reviewed the Arizona State University's (ASU) June 25, 2007 and June 26, 2007 responses to OHRP's letter dated May 15, 2007 regarding allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human subjects (45 CFR part 46) involving the above-referenced research.

In its letter dated May 15, 2007, OHRP made the following determinations regarding the above-referenced research:

1) OHRP found that an unanticipated problem involving risks to subjects or others and an instance of continuing noncompliance were not reported to OHRP as required by HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5).

   Corrective Actions: OHRP notes that ASU has updated its policies that address reporting of unanticipated problems. Also, OHRP acknowledges ASU's statement that it now requires mandatory training for all investigators involved in human subjects research. OHRP acknowledges receipt of an incident reports for the instance of continuing noncompliance referenced above.

2) HHS regulations at 45 CFR 46.109(e) require that continuing review of research be conducted by the institutional review board (IRB) at intervals appropriate to the degree of risk, but not less than once per year. OHRP found that the ASU IRB failed to conduct continuing review at least once per year for one study which resulted in a lapse in IRB approval.

   Corrective Actions: ASU indicated that it has administrative procedures in place for verifying approval and expiration dates during preliminary protocol review by an IRB staff member. ASU also indicated that all IRB approval documents to the investigator now contain approval and expiration dates, and that reminder notices are sent to investigators prior to study expiration. OHRP notes that ASU stated that investigators are reminded of their responsibility to submit continuing review materials in advance of

the study expiration date, regardless of the courtesy reminders sent.

3) HHS regulations at 45 CFR 46.115(a)(4) require that an institution, or when appropriate an IRB, prepare and maintain adequate documentation of IRB activities, including copies of all correspondence between the IRB and the investigators. OHRP found that ASU IRB protocol records for two studies did not include this information stipulated at 45 CFR 46.115(a)(4).

   Corrective Actions: ASU stated that the staff of the Research Compliance Office providing support for the record-keeping function of the IRB are now trained and responsible for ensuring that study files are maintained in accordance with the regulations. OHRP acknowledges receipt of an incident report for the noncompliance referenced above.

4) HHS regulations at 45 CFR 46.110(c) require that each IRB which uses an expedited review procedure shall adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

   OHRP found that ASU IRB members were not advised that the study entitled "Gila River Diabetes Reduction Initiative," HS #0509000171, had been approved at initial and continuing review using expedited review procedures.

   Corrective Action: ASU stated that the IRB now receives a monthly report, generated from the IRB database, listing studies that were approved by expedited procedures. This report includes the principal investigator's name, title of the research, categories of review, and approval dates and is distributed to each IRB members with their protocol review materials.

OHRP makes the following additional determinations:

5) OHRP finds that the ASU IRB approved the research referenced below contingent upon substantive modifications or clarifications that are directly relevant to the determinations required by the IRB under HHS regulations at 45 CFR 46.111 without requiring additional review by the convened IRB.

   In specific, OHRP notes that the minutes of the March 7, 2006 IRB meeting contain, in pertinent part, the following information for the protocol entitled "Physiological and Psychological Effect of an Acupuncture Intervention in Normal Healthy Students," HS # 0602000664: "After discussion, the IRB approved the protocol with the following minor stipulations that will be reviewed and approved by the staff and <the primary reviewer>:

   - Application – Provide an extensive list of inclusion/exclusion criteria. Specifically describe use of what medications and conditions would constitute exclusion….

- For question 10c, clarify what you mean by current level of fitness. Are certain individuals being included or excluded?...

- In question 11a, clarify what steps will be taken to minimize the risks as described to the IRB.

Corrective Actions: OHRP notes that the ASU "Procedures for the review of human subjects research," revision date 6/11/07, contains the following language:

> Require modifications in (to secure approval) -
>
> The IRB approves a protocol with specific conditions that must be met by the PI before proceeding with the protocol….If the modifications are minor, the IRB Chair or primary reviewer may approve the study upon receipt of the satisfactory revisions. As part of its vote and deliberation, the IRB indicates whether the modifications are considered minor or substantial… Modifications are considered minor if they will not change the risk to the participant regardless of the response.
>
> If modifications are considered to be substantial, meaning that the study does not meet criteria for approval as defined by 45CFR46.111, the IRB requires that the modifications be reviewed by the convened IRB, the IRB requires that the modifications be reviewed by the convened IRB. As part of its deliberation, the IRB will discuss whether any revisions to the IRB application, informed consent document or other documents will require review by the convened IRB. As part of its deliberation, the IRB will discuss if the risk-benefit ratio can be assessed. In cases where this is not possible, the modifications will require review by the convened IRB. The vote will reflect whether the changes must be reviewed by the convened IRB.

HHS regulations at 45 CFR 46.109(a) state that IRBs reviewing research have authority to approve, require modifications in (to secure approval) or disapprove the research. When ASU determines that "required modifications are substantial" and "defers to reconsideration by the convened IRB," OHRP would consider ASU to be "requiring modifications to secure approval" and the study can not be approved at that meeting. Further, if the IRB, at a convened meeting, cannot assess the risk-benefit ratio of a study based on the information provided, the IRB can not approve the study at that meeting. The IRB may require modifications to secure approval and these modifications may be reviewed and the modified study may be approved at a subsequent convened meeting.

OHRP notes that when the convened IRB requests clarifications or modifications regarding the protocol or informed consent documents that are required for the IRB to make any the determinations required under HHS regulations at 45 CFR 46.111, not just those related to the risk/benefit ratio, IRB approval of the proposed research must be deferred, pending subsequent review by the convened IRB of responsive material. However, when the ASU IRB decides to require only "minor modifications," the action

taken by the IRB at the convened meeting would be considered an approval of the research with conditions, not "requiring modifications to secure approval."

When the convened IRB approves research with conditions, the approval is deemed to have occurred at the meeting during which the conditions were stipulated. OHRP notes that the following statement from ASU procedures is not accurate, since a study is deemed to have been already approved at the convened meeting: "If the modifications are minor, the IRB Chair or primary reviewer may approve the study upon receipt of the satisfactory revisions." If a study is approved by the IRB with conditions, under the current ASU procedure the research may not proceed until the response from the investigator(s) has been reviewed and accepted by the designated IRB reviewer. OHRP notes that the IRB reviewer is not "approving" the study, but rather determining whether the investigator's response adequately addresses the IRB's conditions.

OHRP recommends that the ASU IRB procedures be revised to accurately reflect the guidance that OHRP provides above.

6) HHS regulations at 45 CFR 46.110(b)(1) limit the use of expedited review procedures to specific research categories published in the *Federal Register* at 63 FR 60364-60367. OHRP finds that the ASU IRB inappropriately applied expedited review to research that appears to involve no more than minimal risk but does not appear in the categories of research published in the *Federal Register* when it initially approved the study entitled "Molecular Regulation of Muscle Glucose Metabolism in Man," HS #0501002211**,** under expedited review category 8. OHRP notes that expedited review category 8 only applies to continuing review of research previously approved by the convened IRB.

OHRP also finds that it was inappropriate to apply two other expedited review categories to this research at the time of continuing review – expedited review categories 5 and 7. Expedited review category 5 involves research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). OHRP notes that the ASU investigator's research activity was solely the analysis of coded data and biological samples obtained for purposes of this specific research study at another institution. Expedited review category 7 involves research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

Corrective Actions: OHRP notes that the complete study record for this research was reviewed by the ASU IRB in June 2007 at a convened meeting, and the IRB determined that the "study activities at ASU are limited to analysis of coded data and samples collected for this study at another institution present no more than minimal risk to subjects, that data collection at the collaborating institution is covered by a valid IRB

approval, that adequate documentation is provided to make a determination and that no risks to subjects were identified as a result of the prior approval under expedited review procedures." ASU stated that "The IRB unanimously voted to approve the study, deferring future review to expedited procedures, if no additional risks are identified, by the expedited review as authorized by 45 CFR 46.110(9), Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) doe not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified."

ASU indicated that "IRB Chairs and members who act as expedited IRB reviewers and staff supporting the IRB have received additional training and educational material explaining the appropriate use of expedited review procedures. A checklist is available for IRB members performing expedited review that gives examples and a brief overview of the types of studies that are eligible and appropriate when making determinations authorized under expedited review procedures, as provided for under federal regulations at 45 CFR 46.110. Staff supporting the record keeping function for the IRB prepare a cover page that suggests categories of expedited review that may be appropriate based in initial review and the IRB reviewer documents the basis for expedited review at the time of approval. The cover page will be maintained in the study record to document the approval process. If one or more of the categories eligible for expedited review cannot be justified, the study is submitted to the convened IRB for review. To ensure the integrity of the expedited review process, the IRB will perform a periodic random audit of studies approved under an expedited review procedure."

OHRP expressed the following concerns in its May 15, 2007 letter to ASU:

7) OHRP expressed concern that the ASU IRB may have improperly determined two studies to be exempt under HHS regulations at 45 CFR 46.101(b), thereby allowing non-exempt research to be conducted without IRB review and approval, in contravention of the requirements of HHS regulations at 45 CFR 46.103(b) and 46.109(a).

   a) The study entitled "Analysis of Blood Samples," HS #0506000016, was determined on April 22, 2006 by the ASU IRB to be exempt as per regulations at 45 CFR 46.101(b)(4). OHRP noted that it appeared that this determination was based in part on the assessment of the IRB that the samples received by the ASU investigator for analysis were "deidentified." OHRP expressed concern that the subjects could be identified through identifiers linked to subjects (i.e., a code) and therefore the exemption at 46.101(b)(4) would not apply.

      ASU Response: The ASU IRB sought additional information from the investigator and reevaluated the study, concluding that the study met the conditions outlined in the OHRP guidance document entitled "Guidance on Research Involving Coded Private Information or Biological Specimens,"

http://www.hhs.gov/ohrp/humansubjects/guidance/cdebiol.htm, allowing the study to be deemed to not be human subjects research.

b) The study entitled "Mechanisms of Protections of HIV-Exposed Seronegative Partners of Seropositive Patients," HS #0407001903, was originally approved by the ASU IRB on July 26, 2004. When the investigator submitted continuing review materials in August 2005, he was advised by the IRB to resubmit the study under an exempt application for use of de-identified data. On September 13, 2005, the IRB determined the study to be exempt as per regulations at 45 CFR 46.101(b)(4). OHRP expressed concern that the data utilized by ASU is coded, not de-identified, therefore the exemption at 46.101(b)(4) would not apply.

ASU Response: The ASU IRB reevaluated this study and determined that the data is in fact rendered deidentified, thereby allowing the study to be eligible for the exemption at 46.101(b)(4).

ASU also stated that "in response to the OHRP questions and the IRB reevaluation of these two studies, the application form for exempt research has been updated to include additional guidance on the criteria for research involving coded private information and biological samples."

8) OHRP expressed concern its May 15, 2007 letter that the ASU IRB should have reported a subject complaint received in November 2005 to OHRP as either an unanticipated problem involving risks to subjects or others, or serious or continuing noncompliance on the part of the research assistant or the investigator. The ASU response framed the issue as a result of the negative credit process used in the course. OHRP asked ASU to investigate whether the subject was prevented from discontinuing participation without penalty, in contravention of HHS regulations at 45 CFR 46.116(a)(8). OHRP also asked whether other ASU studies involve the "negative credit process" mentioned in ASU's response. Further, OHRP disputed ASU's statement that reporting to OHRP on this study was not required, given that the project is not federally funded. OHRP noted that during the time period in which this incident occurred, the ASU FWA in effect at that time was applicable to all research involving human subjects, regardless of sponsorship.

Corrective Actions: OHRP acknowledges ASU's assessment that the issue involved was solely related to the negative credit process and that as a result of the IRB inquiry related to this subject complaint, the negative credit process for the ASU West PGS 101 Experimentrak Subjects Pool has been abandoned and that there is no negative credit process for any other ASU IRB-approved studies.

ASU stated that "it is the view of the ASU IRB that student participation in a research study must be entirely voluntary and that withdrawal at any stage (including before actual participation begins as in the case of a subject pool) in the process cannot carry a penalty." ASU also stated:

Students selecting the research participation option understand the requirements for registration, withdrawal and the cancellation policy from the start. The negative consequences for not showing up for or cancelling a scheduled appointment is transparent to students from the start, and is assessed for reserving a spot that could have been assigned to another student. Exceptions to the cancellation policy are made when circumstances outside of the student's control prevented them from keeping the appointment or giving advance notice of withdrawal.

OHRP finds that the corrective actions and responses above adequately address the above findings and concerns and are appropriate under ASU's assurance. As a result, there should be no need for further involvement of OHRP in this matter. Of course, OHRP must be notified should new information be identified which might alter this determination.

OHRP appreciates the continued commitment of your institution to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Karena Cooper, JD, MSW
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Susan Metosky, IRB Administrator, ASU
Debra Murphy, Research Compliance Office, ASU
Dr. Mike Roosa, ASU IRB #1 Chairperson
Dr. Anna Schwartz, ASU IRB #2 Chairperson
Dr. Bernard Schwetz, OHRP
Dr. Melody H. Lin, OHRP
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Dr. Kristina Borror, OHRP
Ms. Shirley Hicks, OHRP
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Ms. Patricia El-Hinnawy, OHRP
Ms. Cathy Slatinshek, OHRP
Ms. Kelley Booher, OHRP
Mr. Barry Bowman, OHRP