DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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April 21, 2004

Raymond S. Greenberg, M.D., Ph.D.
President
Medical University of South Carolina
171 Ashley Avenue
Charleston, SC 29425

RE: Human Research Subject Protections Under Federalwide Assurance (FWA) 00001888

Research Activity: Alpha-1 Research Registry
Principal Investigator: Dr. Charles Strange
Project Number: HR #9059

Dear Dr. Greenberg:

The Office for Human Research Protections (OHRP) has reviewed the Medical University of South Carolina's (MUSC) report dated February 25, 2004, responding to allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46) in the above-referenced research.

Based upon its review of the February 25, 2004 report, OHRP makes the following determinations with regard to operations of the Alpha-1 Research Registry (the Registry):

(1) HHS regulations at 45 CFR 46.116(a)(5) require that informed consent documents include a statement describing the extent to which confidentiality of records identifying the subject will be maintained.

It was alleged that the methods employed by the researchers to protect the confidentiality of the research data and the privacy of subjects varied from the methods described in the informed consent document entitled, "Research Questionnaire/Consent to Participate in the Alpha-1 Research Registry" (the Alpha-1 informed consent document) and from the information found on the Alpha-1 Foundation Web site (the Alpha-1 web site). It was alleged that the methods actually used to collect and store the data offered less protection of privacy and confidentiality than was described to subjects.

Corrective Action:
OHRP acknowledges the changes made by MUSC to protect the confidentiality of the Registry's research data and to maintain confidentiality in the manner described to research subjects. OHRP notes that the MUSC Institutional Review Board (IRB) took most of the steps to enhance the protection of the data prior to OHRP's involvement in this matter. In specific, OHRP acknowledges that the Registry computer is now housed in a locked room at MUSC, with a second computer located in the Registry Coordinator Center office. MUSC states that both computers require multiple passwords, and that paper records used by the Registry are kept in locked file cabinets within locked rooms at MUSC.

According to your February 25, 2004 report, the Registry currently uses an encrypted intranet with a double firewall. Data is housed exclusively on the computer and does not use the MUSC server. Study coordinators accessing the Registry at national meetings now use an encrypted internet connection via an encrypted intranet connection, and access the Registry only in locations where private identifiable information cannot be seen or heard by others. Finally, OHRP acknowledges that according to your report, the researchers have applied for a certificate of confidentiality from the National Institutes of Health/National Heart, Lung, and Blood Institute.

OHRP finds that these corrective actions adequately address the above allegation and are appropriate under the MUSC FWA.

(2) 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. HHS regulations at 45 CFR 46.116(a) delineate the specific elements required for informed consent. OHRP finds that the Alpha-1 informed consent document failed to include all the elements of informed consent required by HHS regulations at 45 CFR 46.116(a). OHRP also finds no evidence that the MUSC IRB found and documented the criteria necessary to waive these elements.

OHRP acknowledges that the MUSC IRB has reviewed and approved a revised informed consent document that includes all elements required for legally effective informed consent under HHS regulations at 45 CFR 46.116(a). In specific, OHRP acknowledges the following revisions to the Alpha-1 informed consent document:

(a) Statements that the study involves research and an explanation of the purposes of the research have been added.

(b) An explanation of whom to contact for answers to pertinent questions about the research and about the rights of research subjects, and information on whom to contact in the event of a research-related injury to the subject have been added.

(c) The section describing participant responsibilities has been amended to remove any language that reflects the possibility of coercion or undue influence.

Required Action:
By June 11, 2004, please provide OHRP with a satisfactory corrective action plan to ensure that the IRB approves informed consent documents that contain all the elements required under HHS regulations at 45 CFR 46.116(a), or finds and documents the criteria to waive these elements as outlined in HHS regulations at 45 CFR 46.116(d).

At this time, OHRP offers the following additional guidance:

(3) OHRP notes that MUSC's written IRB procedures require reporting to OHRP when a study should be suspended or terminated due to "serious or continuing noncompliance." However, HHS regulations at 45 CFR 46.103(a) and 46.103(b)(5) require institutions to have written procedures for ensuring prompt reporting of any unanticipated problems involving risks to subjects or others, any serious or continuing noncompliance with HHS policies or the requirements or determinations of the IRB, or any suspension or termination of IRB approval. The regulations do not limit reporting of unanticipated problems involving risks to subjects or others to "serious or continuing noncompliance."
For example, if a potential breach of confidentiality of research data occurs, the IRB should make the determination whether this is an unanticipated problem involving risks to subjects or others that requires reporting to OHRP. OHRP recommends that MUSC review its procedures for reporting unanticipated problems to OHRP, and that MUSC take steps to inform its investigators and the IRB of the rules for reporting to the IRB and to OHRP following such a determination.

(4) OHRP recommends that MUSC remind investigators that HHS regulations at 45 CFR 46.103(b)(4)(iii) require IRBs to 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 appreciates MUSC's commitment to the protection of human research subjects. Please do not hesitate to contact me should you have any questions.

Sincerely,

Rina Hakimian, J.D., M.P.H.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Becky Roberts, IRB Administrator, MUSC
Dr. Patricia Arford, Chair, IRB I & II, MUSC
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