DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

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June 5, 2009

Joseph J. Ferretti, Ph.D.
Senior Vice President and Provost
Board of Regents of the University of
Oklahoma Health Sciences Center
1000 Stanton L. Young Blvd., Rm. 221
Oklahoma City, OK 73117-1213

RE: **Human Research Protections Under Federalwide Assurance FWA-7961**

Research Project: **A Phase III Study for the Treatment of Children and Adolescents with Newly Diagnosed Low Risk Hodgkin Disease**
Principal Investigator: **Rene McNall, M.D.**
HHS Protocol Number: **COG AHOD0431**

Dear Dr. Ferretti:

Thank you for your March 31, 2009 report in response to our March 2, 2009 determination letter and our request that the University of Oklahoma Health Sciences Center (UOHSC) evaluate additional allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

Based on the information submitted, we make the following determinations:

A. Determinations Regarding the Above-Referenced Research:

(1) HHS regulations at 45 CFR 46.116(a) require that when seeking informed consent specific information shall be provided to each subject unless the institutional review board (IRB) approves a consent procedure which does not include, or which alters, some or all of the required basic elements of informed consent provided in accordance with 45 CFR 46.116 (c) or (d). From the material presented in your response, we determine that the UOHSC IRB-approved informed consent documents for the above-referenced study failed to include a complete explanation of the purposes of the research and identification of procedures which were experimental (as required by 45 CFR 46.116(a)(1)) and that the UOHSC IRB did not waive or alter such elements in accordance with 45 CFR

46.116(d). In particular, we find that none of the UOHSC IRB-approved informed consent documents included one of the secondary aims of the study, i.e. to determine the prognostic significance of very early response as measured by Fludeoxyglucose - Positron emission tomography (FDG-PET) or gallium scans after the first course of chemotherapy. In addition, we find that the UOHSC IRB-approved informed consent forms failed to identify that the performance of such scans after the first course of chemotherapy appears to be experimental. See sections 1.1.5, 1.2.4, 2.6, 17.2.1 and 17.2.2 of the UOHSC IRB-approved protocol.

(2) A complainant alleged, and we determine, that the informed consent document for this study failed to include an adequate description of any reasonably foreseeable risks and discomforts, as required by HHS regulations at 45 CFR 46.116(a)(2). In particular, we determine that the UOHSC IRB-approved informed consent documents for the above-referenced study failed to include the risks and discomforts associated with additional FDG-PET or gallium scans being conducted during adriamycin (doxorubicin), vincristine, prednisone, cyclophosphamide (AV-PC) (see discussion above) and that the UOHSC IRB did not waive or alter this element in accordance with 45 CFR 46.116(d).

Corrective Actions: We acknowledge your explanation that (a) UOHSC followed the consent form for the above-referenced research that was reviewed and approved by the Cooperative Oncology Group (COG) and the National Cancer Institute's (NCI's) Pediatric Central IRB, and (b) this consent form was silent regarding the secondary aims of the study related to the FDG-PET and gallium scans and the risks and discomforts of these scans. Please note that we have brought the deficiencies in the informed consent document that was approved by the NCI's Pediatric Central IRB to the attention of appropriate officials at NCI. NCI has informed us that they have taken a number of actions to address these deficiencies including developing plans to (a) communicate to all subjects enrolled in the study the study aim of determining the prognostic significance of FDG-PET or gallium scans after the first course of therapy and that this is not standard practice in the treatment of Hodgkins Disease in children; and (b) examine NCI's review processes (through the Cancer Therapy Evaluation Program and the Pediatric CIRB) to understand how these deficiencies happened and to prevent them from happening in the future. While we have not been provided with an informed consent form for this study that has been modified to remedy the deficiencies we found, we note that as of December 5, 2008 the study was temporarily closed to accrual to allow for collection, review and analysis of current data. We expect that if the study is reopened, the above changes will be made to the informed consent document. We determine that these actions adequately address the informed consent deficiencies identified during our review of UOHSC's involvement in this research.

(3) The complainant alleged that the investigator only performed 5 immunophenotyping panels, even though the protocol exclusion criteria called for immunophenotyping with a minimum panel of 11, without first obtaining IRB review and approval of this change in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii). This regulation provides that

an IRB must 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.

We determine that this allegation could not be proven. UOHSC responded that section 16.2 of the UOHSC IRB-approved protocol provided that for eligibility in this protocol a recommended minimum panel of antibodies should include: CD45, CD3, CD20, CD15 and CD30. UOHSC further stated that, in accordance with the UOHSC IRB-approved protocol, the investigators conducted the following antibody panel to test the complainant's child pathology specimen: CD 45, CD3, CD20, CD30, CD15 and CD5. UOHSC provided our office with a copy of the pathology report documenting these actions.

(4) From the material presented in your response, we determine that the investigator implemented the following changes without first obtaining IRB review and approval of these changes in the research in violation of HHS regulations at 45 CFR 46.103(b)(4)(iii).

(a) The investigator failed to notify two subjects currently on study of the drug toxicity changes associated with Filgrastim. We noted that during the August 13, 2007 UOHSC IRB meeting, the UOHSC IRB contingently approved protocol amendment #1 to the above-referenced study; the contingency being that the investigator notify the two "patients" currently on study of the drug toxicity changes associated with Filgrastim. UOHSC informed our office that the investigator: (a) decided not to notify the two patients of the drug toxicity information because at the time the amendment was approved the subjects had completed the therapy involving the drug Filgrastim; and (b) never notified the UOHSC IRB of the investigator's decision. We appreciate and acknowledge UOHSC's statement that the investigator should have notified the IRB when the investigator decided not to notify the enrolled subjects so that the IRB could determine whether its initial approval was affected by the change.

(b) The investigator failed to provide the complainant's son with prophylaxis for pneumocysti carinii pneumonia (PCP) as indicated in section 8.2 of the IRB-approved protocol (version date October 19, 2005). The complainant alleged that her son was never informed that he was to receive antibiotics prophylactically, and her son did not receive any further antibiotic treatment once the initial prescription was finished despite continuing chemotherapy. According to the complainant an antibiotic prescription was dispensed by a UOHSC attending physician on May 10, 2007 prior to her son enrolling into the trial on May 14, 2007. The UOHSC responded that the complainant's son, while initially given Bactrim to treat a cellulitis, was never started on PCP prophylaxis as required by the protocol.

Required Action: Please provide our office with a corrective action that will ensure that investigators do not implement 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.

(5) The complainant alleged that the UOHSC investigators failed to provide the complainant and/or her son with a signed copy of the informed consent form, as indicated in the informed consent document. Please note that 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 and signed by the subject or the subject's legally authorized representative unless the requirement for documentation of informed consent has been waived by the IRB in accordance with HHS regulations at 45 CFR 46.117(c). The regulations provide further that a copy of the informed consent document shall be given to the person signing the form.

UOHSC provided the following response:

> "All participant families received two copies of the informed consent form at the time of initial protocol discussions. This is standard operating procedure at the University. When the complainant returned to enroll her child, she provided a signed consent document. We have no documentation to support our position that a copy of this signed document was provided to the complainant. That is the University's standard practice, however. At no time did she request a copy or otherwise indicate she did not receive one, in which case the University would have promptly provided one. A signed copy was forwarded to her home address via registered mail on March 30, 2009."

Given UOHSC's response that the standard institutional practice is to provide subjects with a copy of the signed informed consent form, and noting that the complainant was provided a copy of the signed informed consent form in March 2009 in response to our communication of this allegation to UOHSC, we cannot determine whether a violation of the regulatory requirements at HHS regulations at 45 CFR 46.117 occurred and thus make no determination of noncompliance in response to this allegation.

B. Questions and Concerns:

(1) [Redacted]

[Redacted]

(2) [Redacted]

[Redacted]

(3) [Redacted]

Please submit your response to the determinations and questions and concerns noted above so that we receive them no later than July 2, 2009. If during your review you identify additional areas of noncompliance with the HHS regulations for the protection of human subjects, please provide corrective action plans that have been or will be implemented to address the noncompliance.

We appreciate your institution's continued commitment to the protection of human research subjects. Please contact me if you should have any questions regarding this matter.

Sincerely,

Lisa A. Rooney, J.D.
Compliance Oversight Coordinator
Division of Compliance Oversight

cc: Ms. Meg R. Ribaudo, Director, Office of Human Research Participant Protection, UOHSC
Dr. Lynn Devenport, IRB Chairperson, University of Oklahoma-Norman IRB #1,
Dr. Karen J. Beckman, IRB Chairperson, UOHSC IRB #1, #3, & #5
Dr. Terry Dunn, IRB Chairperson, UOHSC IRB #2
Dr. Martina Jelley, IRB Chairperson, UOHSC IRB #4
Dr. Laurette Taylor, IRB Chairperson, University of Oklahoma – Norman IRB #2
Dr. Rene McNall, Department of Pediatrics, UOHSC
Dr. Joshua M. Sharfstein, Acting Food and Drug Administration (FDA) Commissioner
Dr. Joanne Less, FDA
Dr. John E. Niederhuber, Director, NCI
Dr. Jeffrey S. Abrams, Acting Associate Director, Cancer Therapy Evaluation Program, NCI
Dr. Sherry Mills, National Institutes of Health (NIH)
Mr. Joseph Ellis, NIH