DEPARTMENT OF HEALTH & HUMAN SERVICES

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March 2, 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 June 19, 2008 report and August 20, 2008 clarification letter in response to our May 2, 2008 request that the University of Oklahoma Health Sciences Center (UOHSC) evaluate allegations of noncompliance with Department of Health and Human Services (HHS) regulations for the protection of human research subjects (45 CFR part 46).

At the outset, we would like to recognize that the above-referenced protocol was a Children's Oncology Group (COG) sponsored protocol, which was reviewed and approved by the Central Institution Review Board (CIRB), an initiative that is sponsored by the National Cancer Institute (NCI). Given this, we acknowledge that some of the questions and concerns noted below are not specific to the UOHSC institutional review board (IRB). Instead, some of the issues identified in this letter raise concerns regarding the protocol and informed consent forms that were reviewed and approved by the CIRB. As a result, we will raise with the CIRB those issues that are specific to the CIRB review and approval process associated with this study.

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

A. Determinations Regarding the Above-Referenced Research:

(1) The complainant alleged that the investigator failed to obtain IRB review and approval for the following changes in the study entitled "A Phase III Study for the Treatment of Children and Adolescents with newly Diagnosed Low Risk Hodgkin Disease," during the period for which IRB approval has already been given, prior to initiating such changes, as required by HHS regulations at 45 CFR 46.103(b)(4)(iii):

(a) The complainant's son underwent CT scans with and without contrast, even though the protocol only calls for CT scans with contrast.

We find that this allegation could not be proven. UOHSC responded that the complainant's son underwent CT scans of the neck, abdomen, chest and pelvis with and without contrast on May 7, 2007 as part of his clinical care and before he consented to participate in the trial on May 14, 2007. According to UOHSC, the complainant's son underwent protocol indicated CT scans to the same areas on July 9, 2007, with contrast only, at the end of his chemotherapy treatment in accordance with Section 7.1.1 of the UOHSC IRB-approved protocol. UOHSC concluded that the only CT scans done with and without contrast were done prior to obtaining informed consent as part of clinical care; thus, there is no evidence indicating that the complainant's son underwent any CT scans in violation of the UOHSC IRB-approved protocol.

(b) The protocol called for a second set of CT scans only at the sites involved at time of diagnosis, but the complainant's son underwent a second set of CT scans of the abdomen and pelvis, which had been cleared in previous scans.

We find that this allegation could not be proven based on the following response provided by UOHSC:

> "According to physicians on the treatment team, it is their practice for patients who have finished therapy for lymphoma to re-assess via diagnostic imaging the entire at-risk sites, not just those previously involved. This is done to ensure that no additional areas of cancer developed during the treatment and to ensure that patient is disease free throughout the body prior to terminating treatment. In this case, the repeat scans of the abdomen and pelvis were clinically indicated for this reason, even though not required by the research protocol. The protocol sets forth the required scans. To obtain additional scans not called for by the protocol as in this case was not a protocol violation because the protocol does not contain language prohibiting additional scans and the scans of the abdomen and pelvis at the conclusion of treatment appear to be clinically indicated as they are a standard practice at this institution. They would have been performed whether or not the subject was participating in the clinical trial. …."

(c) The protocol states that only FDG-PET is to be used, but the complainant's son underwent FDG-PET/CT scans.

We find that this allegation could not be proven. UOHSC responded that the complainant's son underwent a FDG-PET/CT scan because of its superiority in anatomic detail over the older style FDG-PET cans. Moreover, UOHSC noted that Appendix II of the UOHSC IRB-approved protocol provided specific details for obtaining FDG-PET/CT for those sites equipped with such scanners. Thus, UOHSC concluded, and we concur, that the use of such scans was allowed under the protocol.

(d) The complainant's son was scheduled for a FDG-PET scan as part of a six-month review, even though the protocol stated FDG-PET is only to be used in the initial stages of the trial.

We find that this allegation could not be proven based on the following response provided by UOHSC:

> "According to physicians on the treatment team, it is their practice for patients who are being re-evaluated at their six-month follow-up for lymphoma that is believed to be in remission, to re-assess via diagnostic imaging the entire at-risk sites, not just those previously involved. In this case, FDG-PET/CT was chosen as the imaging modality. Furthermore, page 2 of the informed document signed by the complainant, reads with regard to the use of FDG-PET: "Some subjects will have additional scans, but it is unlikely you will have more than four scans during this treatment." This order for a third FDG-PET/CT (which was not performed) was clinically indicated and therefore neither a protocol violation nor a potential noncompliance with regulations for the protection of human research subjects."

(e) The complainant's son received two Gallium scans, even though they were not indicated by the protocol.

We find that this allegation could not be proven based on section 17.2 of the protocol which provides the following: "Two nuclear medicine modalities are acceptable for this study, although [18F]-Fluorodeoxyglucose (FDG) imaging is strongly encourage. Gallium will only be acceptable when FDG is not available. These are gallium scintigraphy and [18F]-Fluorodeoxyglucose (FDG) imaging. Whichever study is used at time of diagnosis should be used at all subsequent evaluation points. As clinically indicated, both studies may be performed." In responding to this allegation, UOHSC queried the physicians on the treatment team as to their opinion on why both modalities would be acceptable. The physicians explained that at the time the protocol was written (activation February 2006) the role of PET scan in Hodgkin's disease had not been clearly delineated; standard practice until then was to obtain a gallium scan. UOHSC continued that the treating team had reasonably limited experience with FDG-PET imaging in Hodgkin's lymphoma in May 2007 given that the imaging modality had been available to the pediatric population for only

approximately 6 months and the number of patients it had been utilized on locally was small. Thus, while gaining experience with this newly available imaging modality, both were being utilized on all patients with suspected or proven lymphoma at the time the complainant's son presented for initial clinical evaluation. This is the clinical indication for the initial dual nuclear studies that were obtained at presentation.

(f) The complainant's son underwent 2 bone marrow biopsies, which are not indicated in the protocol. According to UOHSC, the complainant's son underwent an initial bone marrow biopsy on May 4, 2007 as part of his clinical diagnostic evaluation prior to staging (and prior to enrolling into the study) and a second bone marrow biopsy after the complainant's son completed treatment.

We find that this allegation could not be proven based on the following response which was provided by UOHSC in its letter dated August 20, 2008:

> "The patient did undergo bilateral (two) bone marrow biopsies and bilateral (two) bone marrow aspirates on May 4, 2007, while under general anesthesia for the lymph node biopsy (the diagnostic procedure) and placement of an infusaport. This procedure was done prior to the diagnosis and as part of evaluation of a suspected malignancy. By performing bone marrow assessment during general anesthesia, the patient is not subjected to a second sedation, should the biopsy prove to be a malignancy that would require bone marrow assessment for staging. The bone marrow aspirates and biopsies were not for any protocol purpose, but solely to stage the patient and avoid sedation for this procedure at a later time, saving the patient increased discomfort (both psychological and physical) from a procedure with sedation, rather than anesthesia. … This was the only bone marrow testing that was done. The patient did not undergo a second bone marrow after completion of therapy, as our initial response stated. The two bone marrow biopsies that were performed were not required by the protocol but were clinically indicated and were therefore neither a protocol violation nor a potential noncompliance with regulations for the protection of human research subjects."

(g) The protocol exclusion criteria excluded "morphologically unclassifiable lymphoma," but the complainant's son's pathology report stated "Classical Hodgkin Lymphoma, favour nodular sclerosis…sub-classification is difficult because the lymph node is fragmented and shows only partial involvement."

We find that this allegation could not be proven. According to UOHSC, the complainant's son's lymphoma was classified as "Classical Hodgkin" and that the lack of sub-classification was not an exclusion criteria in the study. Thus, the complainant's son was eligible for enrollment into the study.

(2) The complainant alleged that there was a failure to ensure that risks to subjects were minimized and that risks to subjects were reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result, as required by HHS regulations at 45 CFR 46.111(a)(1) and (2). In specific, the complainant alleged that:

(a) Unnecessary scans as noted above exposed the complainant's son to higher than necessary levels of radiation, which increases the risk for future cancers.
We find that this allegation could not be proven based on the following response which was provided by UOHSC in its letter dated August 20, 2008:

> "In reviewing the medical records and the protocol, the IRB investigating team found that the only potentially unnecessary scan was the repeat CT scan of the neck performed on May 7, 2007. As mentioned …, this study [CT scan] was repeated 10 days prior to enrollment in the clinical trial; thus, it would not fall under the HHS guideline for protection of research subjects. The other diagnostic studies obtained during and after treatment, while not all required by the research protocol, were clinically indicated and appropriate diagnostic scans. Furthermore, all of these were allowable by the protocol, some at the discretion of the treatment physician. The informed consent document signed by the complainant contains language such that the subject might undergo more diagnostic scans than were performed in this case, and at more frequent intervals.
>
> In responding to this allegation, it is essential to put it into context. The complainant's son was diagnosed with Hodgkin Disease. The standard treatment for this disease at UOHSC and across the country is chemotherapy plus radiation. … As pointed out on page 1 of the informed consent document signed by the complainant, treatment without radiation therapy is considered experimental, and treatment without radiation therapy was not listed as an option outside of the research protocol (page 11). As the complainant points out, increased radiation exposure increases future risk of second cancers developing. Thus, the potential benefit of sparing a subject the exposure of therapeutic radiation therapy is significant and would justify some risk of possible higher rates of relapse during the trial. In this particular case, the potential benefit was realized, as the complainant's son did achieve a complete response to chemotherapy and therefore was spared therapeutic radiation therapy.
>
> In assessing this allegation, it is important to realize that the cumulative dose of radiation therapy that the subject was exposed to through all of the diagnostic imaging performed prior to, during the time he was undergoing treatment on the protocol, and at the end of treatment was substantially lower

than the exposure he would have received had he not participated in the clinical trial and been treated with standard care, which would have included both chemotherapy and therapeutic radiation therapy to the neck.

It is therefore concluded that the total amount of radiation exposure for complainant's son for the period of time May – December 2007 was not higher than necessary. Rather, it was less than he would have sustained had he not participated in the clinical trial. Furthermore, all diagnostic scans obtained after enrollment in the study were clinically appropriate and necessary."

(b) The secondary objective of the study is to evaluate FDG-PET as a prognostic indicator in children. The complainant alleged that this leads to exposures in children that exceed NCCN and ACR guidelines, particularly considering evidence that exposure to ionizing radiation should be kept to a minimum in the pediatric population**.**

We find that this allegation could not be proven based on the following response which was provided by UOHSC in its letter dated August 20, 2008:

"In reviewing the protocol, the HHS regulations and information available from the NCCN and ACR, the IRB investigating team found the following information was found pertinent to this complaint:

The National Comprehensive Cancer Network guidelines version 2.2008 was reviewed at http://nccn.org/professionals/physician_gls/pdf/hodgkins.pdf. The overview found on page MS-1 of this document states "These guidelines discuss the clinical management of CHL and LPHO, focusing exclusively on patients from postadolescence through the seventh decade of life who do not have serious intercurrent disease. The guidelines do not address HL in pediatric or elderly patients or those with unusual situations, such as HIV positivity or pregnancy. … .

The complainant alleges her son was exposed to radiation doses that exceed NCCN guidelines; however, these guidelines are for a different population (adult patients) and are therefore not applicable to the complainant's son (a pediatric patient). Because of this, there is not a way to compare radiation exposure for pediatric study subjects to the exposure recommended for the population in the NCCN guidelines to determine if the dose was excessive.

The ACR guidelines referred to in the complainant's letter were sought. Reference 8 was found to be a non-existent web page. Information was reviewed as relevant to this complaint form the following ACR resources: http://www.acr.org/secondaryMainMenuCategories/quality_safety/guidelines/

nuc_med.aspx;
http://www.acr.org/secondarymainmenucategories/quality_safety/guidelines/nuc_med/fdg_pet_ct.aspx and
http://www.acr.org/secondarymainmenucategories/quality_safety/app_criteria/pdf/expertpanelonradiationoncologyhodgkinsworkgrou/pediatrichodgkinsdiseasedoc4.aspx (the latter being reference 5 in the complainant's letter). From review of these documents, no recommended amount of radiation exposure was found for pediatric Hodgkin Disease patients whereby assessment of excessive exposure could be quantified. The disclaimer on every page of the ACR document clearly states: "These criteria are intended to guide radiologist, radiation oncologist and referring physicians in making decisions regarding radiologic imaging and treatment. Generally, the complexity and severity of a patient's clinical condition should dictate the selection of appropriate imaging procedures or treatments. … The ultimate decision regarding the appropriateness of any specific radiologic examination or treatment must be made by the referring physician and radiologist in light of all the circumstances presented in an individual examination."

From this statement by the ACR, the measure of excessive exposure would be radiation exposure that was not clinically indicated. As discussed above …, there were clinical indications for all of the scans that were ordered; thus, there was not excessive exposure.

Review of the ACR Appropriateness Criteria also shed significant insight into the rationale behind the treatment physician's practice in May 2007 of obtaining both a gallium scan and FDG-PET. The expert panel on Radiation Oncology – Hodgkin's Disease by Louis S. Constine, page 13, states: "Nuclear imaging with gallium-67 was widely used to stage and monitor treatment response in children with HD … FDG-PET has advantages over gallium-67 because the scan is a 1-day procedure with higher resolution, better dosimetry, less intestinal activity, and had a quantization potential … To date, no prospective trials evaluating FDG-PET in pediatric HD have been reported."

This statement underscores the importance of the knowledge that will be obtained from studies such as the one the complainant's son was enrolled in, to give definitive insight into the role of FDG-PET in pediatric Hodgkin Disease. From this, one could also reasonably conclude that while the role of FDG-PET is emerging, it is appropriate to order both the gallium and FDG-PET studies, as allowed by the protocol on page 67, section 17.2, and as included on pages 2 and 3 of the informed consent document signed by the complainant. Obtaining imaging with both modalities was the practice at UOHSC when the complainant's son presented for both initial diagnostic evaluation in suspected lymphoma patients prior to enrollment in a clinical

trial and for follow-up after treatment, whether or not patients were treated as part of a clinical trial."

B. Questions and Concerns Regarding the Above-Referenced Study

In addition to the matter complained about, we have the following questions and concerns regarding the above-referenced study:

(1) [Redacted]

(2) [Redacted]

[Redacted]

(3) [Redacted]

(4) [Redacted]

(5) [Redacted]

C. Additional allegations regarding the above-referenced study:

[Redacted]

(1) [Redacted]

(2) [Redacted]

(3) [Redacted]

(4) [Redacted]

Consistent with its obligations under HHS regulations at 45 CFR 46.115(b) and under Public Law 99-158, I am requesting that your institution investigate this matter and forward to us a written report of its investigation (see OHRP Compliance Oversight Procedures dated October 19, 2005 at http://www.hhs.gov/ohrp/compliance/ohrpcomp.pdf).

Please submit your response to the findings, questions and concerns and additional allegation noted above so that we receive them no later than March 31, 2009. If during your review you identify additional areas of noncompliance with 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
Acting, Food and Drug Administration (FDA) Commissioner
Dr. Joanne Less, FDA
Dr. John E. Niederhuber, Director, National Cancer Institute
Dr. Jeffrey S. Abrams, Acting Associate Director, Cancer Therapy Evaluation Program, NCI
Dr. Sherry Mills, NIH
Mr. Joseph Ellis, NIH